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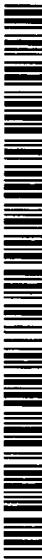
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(54) Title: CHEMICAL COMPOUNDS AND COMPOSITIONS AND THEIR USE AS CATHEPSIN S INHIBITORS

(57) Abstract: The present invention relates to novel selective cathepsin S inhibitors, the pharmaceutically acceptable salts and *N*-oxides thereof, their uses as therapeutic agents and the methods of their making.

CHEMICAL COMPOUNDS AND COMPOSITIONS AND THEIR USE AS CATHEPSIN S INHIBITORS

THE INVENTION

5 This Application relates to compounds and compositions for treating diseases associated with cysteine protease activity, particularly diseases associated with activity of cathepsin S.

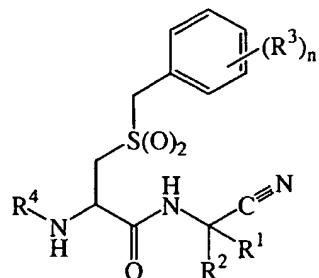
DESCRIPTION OF THE FIELD

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 Cysteine proteases represent a class of peptidases characterized by the presence of a cysteine residue in the catalytic site of the enzyme. Cysteine proteases are associated with the normal degradation and processing of proteins. The aberrant activity of cysteine proteases, e.g., as a result of increase expression or enhanced 15 activation, however, may have pathological consequences. In this regard, certain cysteine proteases are associated with a number of disease states, including arthritis, muscular dystrophy, inflammation, tumor invasion, glomerulonephritis, malaria, periodontal disease, metachromatic leukodystrophy and others. An increase in cathepsin S activity contributes to the pathology and/or symptomatology of a number of 20 diseases. Accordingly, molecules that inhibit the activity of cathepsin S protease are useful as therapeutic agents in the treatment of such diseases.

SUMMARY OF THE INVENTION

This Application relates to compounds of Formula I:



I

5

in which:

n is 1, 2, 3, 4 or 5;

R¹ is hydrogen and R² is cyano, hetero(C₅)aryl or (C₁₋₄)alkyl-substituted hetero(C₅)aryl or both R¹ and R² are hydrogen, halo, (C₁₋₄)alkyl or -X¹OR⁵, wherein X¹ and R⁵ are as defined below, or R¹ and R² together with the carbon atom to which both R¹ and R² are attached form (C₃₋₈)cycloalkylene or (C₃₋₈)heterocycloalkylene;

R³ at the first occurrence is selected from a group consisting of nitro, -X¹NR⁵R⁵, -X¹SR⁵, -X¹C(O)NR⁵R⁵, -X¹C(O)OR⁵, -X¹S(O)R⁶, -X¹S(O)₂R⁶, -X¹C(O)R⁶ and -X¹OR⁷, wherein X¹ is a bond or (C₁₋₂)alkylene, R⁵ at each occurrence independently is hydrogen, (C₁₋₃)alkyl or halo-substituted (C₁₋₃)alkyl, R⁶ is (C₁₋₃)alkyl or halo-substituted (C₁₋₃)alkyl and R⁷ is halo-substituted (C₁₋₃)alkyl and R³ at each other occurrence, if present, independently is selected from a group consisting of (C₁₋₄)alkyl, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X¹NR⁵R⁵, -X¹OR⁵, -X¹SR⁵, -X¹C(O)NR⁵R⁵, -X¹C(O)OR⁵, -X¹S(O)R⁶, -X¹S(O)₂R⁶ and -X¹C(O)R⁶, wherein X¹, R⁵ and R⁶ are as defined above; and

R⁴ is -C(O)X²R⁸ or -S(O)₂X²R⁸, wherein X² is a bond, -O- or -NR⁹-, wherein R⁹ is hydrogen or (C₁₋₆)alkyl, and R⁸ is (i) (C₁₋₆)alkyl optionally substituted by -OR¹⁰, -SR¹⁰, -S(O)R¹⁰, -S(O)₂R¹⁰, -C(O)R¹⁰, -C(O)OR¹⁰, -C(O)NR¹⁰R¹¹, -NR¹⁰R¹¹, -NR¹¹C(O)R¹⁰, -NR¹¹C(O)OR¹⁰, -NR¹¹C(O)NR¹⁰R¹¹ or -NR¹¹C(NR¹¹)NR¹⁰R¹¹, wherein R¹⁰ is (C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl,

hetero(C₅₋₁₂)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₂)aryl(C₀₋₃)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₃)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₃)alkyl and R¹¹ at each occurrence independently is hydrogen or (C₁₋₆)alkyl, or (ii) C₃₋₁₂cycloalkyl(C₀₋₃)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₂)aryl(C₀₋₃)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl,

5 (C₉₋₁₂)bicycloaryl(C₀₋₃)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₃)alkyl or (iii) (C₃₋₆)cycloalkyl(C₀₋₃)alkyl, hetero(C₅₋₆)cycloalkyl(C₀₋₃)alkyl, phenyl(C₀₋₃)alkyl or hetero(C₅₋₆)aryl(C₀₋₃)alkyl substituted by -X³OR¹², -X³SR¹², -X³S(O)R¹², -X³S(O)R₂R¹², -X³C(O)R¹², -X³C(O)OR¹², -X³C(O)NR¹²R¹³, -X³NR¹²R¹³, -X³NR¹³C(O)R¹², -X³NR¹³C(O)OR¹², -X³NR¹³C(O)NR¹²R¹³ or

10 -X³NR¹³C(NR¹³)NR¹²R¹³, wherein X³ is a bond or methylene, R¹² is (C₃₋₆)cycloalkyl(C₀₋₃)alkyl, hetero(C₅₋₆)cycloalkyl(C₀₋₃)alkyl, phenyl(C₀₋₃)alkyl or hetero(C₅₋₆)aryl(C₀₋₃)alkyl and R¹³ is hydrogen or (C₁₋₆)alkyl; wherein R⁴ optionally further contains 1 to 5 substituents which when occurring within an alicyclic or aromatic ring system are radicals independently selected from a group consisting of

15 (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₃)alkyl, nitro, -X⁴NR¹⁴R¹⁴, -X⁴NR¹⁴C(O)OR¹⁴, -X⁴NR¹⁴C(O)NR¹⁴R¹⁴, -X⁴NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -X⁴OR¹⁴, -X⁴SR¹⁴, -X⁴C(O)OR¹⁴, -X⁴C(O)NR¹⁴R¹⁴, -X⁴S(O)₂NR¹⁴R¹⁴, -X⁴P(O)(OR¹⁴)OR¹⁴, -X⁴OP(O)(OR¹⁴)OR¹⁴, -X⁴NR¹⁴C(O)R¹⁴, -X⁴S(O)R¹⁵, -X⁴S(O)₂R¹⁵ and -X⁴C(O)R¹⁵ and when occurring within an aliphatic moiety are

20 radicals independently selected from a group consisting of cyano, halo, nitro, -NR¹⁴R¹⁴, -NR¹⁴C(O)OR¹⁴, -NR¹⁴C(O)NR¹⁴R¹⁴, -NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -OR¹⁴, -SR¹⁴, -C(O)OR¹⁴, -C(O)NR¹⁴R¹⁴, -S(O)₂NR¹⁴R¹⁴, -P(O)(OR¹⁴)OR¹⁴, -OP(O)(OR¹⁴)OR¹⁴, -NR¹⁴C(O)R¹⁵, -S(O)R¹⁵, -S(O)₂R¹⁵ and -C(O)R¹⁵, wherein X⁴ is a bond or (C₁₋₆)alkylene, R¹⁴ at each occurrence independently is hydrogen, (C₁₋₆)alkyl or

25 halo-substituted (C₁₋₃)alkyl and R¹⁵ is (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl; and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

30 A second aspect of the invention is a pharmaceutical composition which

contains a compound of Formula I or a *N*-oxide derivative, individual isomer or mixture of isomers thereof, or a pharmaceutically acceptable salt thereof, in admixture with one or more suitable excipients.

A third aspect of the invention is a method for treating a disease in an animal in
5 which inhibition of cathepsin S can prevent, inhibit or ameliorate the pathology and/or symptomatology of the disease, which method comprises administering to the animal a therapeutically effective amount of compound of Formula I or a *N*-oxide derivative, individual isomer or mixture of isomers thereof; or a pharmaceutically acceptable salt thereof.

10 A fourth aspect of the invention is the processes for preparing compounds of Formula I and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts thereof.

15 DETAILED DESCRIPTION OF THE INVENTION

Definitions:

Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meanings.

"Alicyclic" means a moiety characterized by arrangement of the carbon atoms in closed non-aromatic ring structures having properties resembling those of aliphatics and may be saturated or partially unsaturated with two or more double or triple bonds.

25 "Aliphatic" means a moiety characterized by a straight or branched chain arrangement of the constituent carbon atoms and may be saturated or partially unsaturated with two or more double or triple bonds.

"Alkyl" represented by itself means a straight or branched, saturated or unsaturated, aliphatic radical having the number of carbon atoms indicated (e.g., (C₁₋₆)alkyl includes methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl,

2-methylallyl, ethynyl, 1-propynyl, 2-propynyl, and the like). Alkyl represented along with another radical (e.g., as in arylalkyl) means a straight or branched, saturated or unsaturated aliphatic divalent radical having the number of atoms indicated or when no atoms are indicated means a bond (e.g., (C₆₋₁₂)aryl(C₀₋₃)alkyl includes phenyl, benzyl, 5 phenethyl, 1-phenylethyl 3-phenylpropyl, and the like).

"Alkylene", unless indicated otherwise, means a straight or branched, saturated or unsaturated, aliphatic, divalent radical having the number of carbon atoms indicated (e.g., (C₁₋₆)alkylene includes methylene (-CH₂-), ethylene (-CH₂CH₂-), trimethylene (-CH₂CH₂CH₂-), tetramethylene (-CH₂CH₂CH₂CH₂-) 2-butenylene

10 (-CH₂CH=CHCH₂-), 2-methyltetramethylene (-CH₂CH(CH₃)CH₂CH₂-), pentamethylene (-CH₂CH₂CH₂CH₂CH₂-) and the like).

"Alkylidene" means a straight or branched saturated or unsaturated, aliphatic, divalent radical having the number of carbon atoms indicated (e.g. (C₁₋₆)alkylidene includes methylene (=CH₂), ethylidene (=CHCH₃), isopropylidene (=C(CH₃)₂), 15 propylidene (=CHCH₂CH₃), allylidene (=CH-CH=CH₂), and the like).

"Amino" means the radical -NH₂. Unless indicated otherwise, the compounds of the invention containing amino moieties include protected derivatives thereof. Suitable protecting groups for amino moieties include acetyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, and the like.

20 "Animal" includes humans, non-human mammals (e.g., dogs, cats, rabbits, cattle, horses, sheep, goats, swine, deer, and the like) and non-mammals (e.g., birds, and the like).

"Aromatic" means a moiety wherein the constituent atoms make up an unsaturated ring system, all atoms in the ring system are *sp*² hybridized and the total 25 number of pi electrons is equal to 4n+2.

"Aryl" means a monocyclic or bicyclic ring assembly (fused or linked by a single bond) containing the total number of ring carbon atoms indicated, wherein each ring is comprised of 6 ring carbon atoms and is aromatic or when fused with a second ring forms an aromatic ring assembly. For example, optionally substituted (C₆₋₁₂)aryl as 30 used in this Application to define R⁴ includes 3-acetylphenyl, 3-*tert*-butoxycarbonylaminomethylphenyl, biphenyl-4-yl, 3-hydroxyphenyl,

4-hydroxyphenyl, 3-methoxyphenyl, naphth-2-yl, 3-phenoxyphenyl, phenyl, and the like.

"Bicycloaryl" means a bicyclic ring assembly containing the number of ring carbon atoms indicated, wherein the rings are linked by a single bond or fused and one, but not both, of the rings comprising the assembly is aromatic, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., (C₉₋₁₂)bicycloaryl includes cyclohexylphenyl, 1,2-dihydronaphthyl, 2,4-dioxo-1,2,3,4-tetrahydronaphthyl, indanyl, indenyl, phenylcyclohexyl, 1,2,3,4-tetrahydronaphthyl, and the like).

"Carbamoyl" means the radical -C(O)NH₂. Unless indicated otherwise, the compounds of the invention containing carbamoyl moieties include protected derivatives thereof. Suitable protecting groups for carbamoyl moieties include acetyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, and the like and both the unprotected and protected derivatives fall within the scope of the invention.

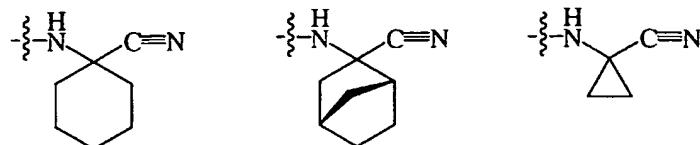
"Carbocyclic ketone derivative" means a derivative containing the moiety -C(O)-.

"Carboxy" means the radical -C(O)OH. Unless indicated otherwise, the compounds of the invention containing carboxy moieties include protected derivatives thereof. Suitable protecting groups for carboxy moieties include benzyl, *tert*-butyl, and the like.

"Cycloalkyl" means a saturated or partially unsaturated, monocyclic ring, bicyclic ring assembly (directly linked by a single bond or fused) or bridged polycyclic ring assembly containing the number of ring carbon atoms indicated, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., (C₃₋₁₂)cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, 2,5-cyclohexadienyl, bicyclohexyl, cyclopentylcyclohexyl, bicyclo[2.2.2]octyl, adamantan-1-yl, decahydronaphthyl, oxocyclohexyl, dioxocyclohexyl, thiocyclohexyl, 2-oxobicyclo[2.2.1]hept-1-yl, and the like).

"Cycloalkylene" means a divalent saturated or partially unsaturated, monocyclic ring or bridged polycyclic ring assembly containing the number of ring carbon atoms indicated, and any carbocyclic ketone, thioketone or iminoketone derivative thereof. For example, the instance wherein "R¹ and R² together with the carbon atom to which

both R¹ and R² are attached from (C₃₋₈)cycloalkylene" includes, but is not limited to, the following:



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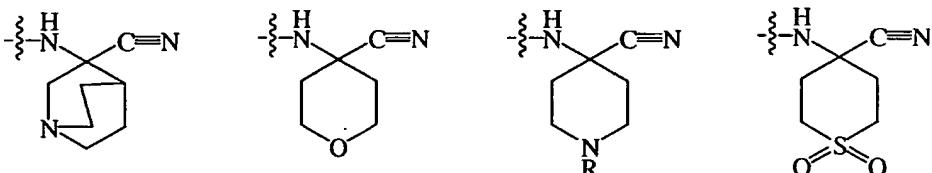
"Disease" specifically includes any unhealthy condition of an animal or part thereof and includes an unhealthy condition that may be caused by, or incident to, medical or veterinary therapy applied to that animal, i.e., the "side effects" of such therapy.

10 "Halo" means fluoro, chloro, bromo or iodo.

"Halo-substituted alkyl", as an isolated group or part of a larger group, means "alkyl" substituted by one or more "halo" atoms, as such terms are defined in this Application. Halo-substituted alkyl includes haloalkyl, dihaloalkyl, trihaloalkyl, perhaloalkyl and the like (e.g. halo-substituted (C₁₋₃)alkyl includes chloromethyl, dichloromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, perfluoroethyl, 2,2,2-trifluoro-1,1-dichloroethyl, and the like).

15 "Heteroatom moiety" includes -N=, -NR-, -O-, -S- or -S(O)₂-, wherein R is hydrogen, (C₁₋₆)alkyl or a protecting group.

20 "Heterocycloalkylene" means cycloalkylene, as defined in this Application, provided that one or more of the ring member carbon atoms indicated, is replaced by heteroatom moiety selected from -N=, -NR-, -O-, -S- or -S(O)₂-, wherein R is hydrogen or (C₁₋₆)alkyl. For example, the instance wherein "R¹ and R² together with the carbon atom to which both R¹ and R² are attached from hetero(C₃₋₈)cycloalkylene" includes, but is not limited to, the following:



25

in which R is hydrogen, (C₁₋₆)alkyl, or a protecting group.

"Heteroaryl" means aryl, as defined in this Application, provided that one or more of the ring carbon atoms indicated are replaced by a heteroatom moiety selected from -N=, -NR-, -O- or -S-, wherein R is hydrogen, (C₁₋₆)alkyl, a protecting group or represents the free valence which serves as the point of attachment to a ring nitrogen, and each ring is comprised of 5 or 6 ring atoms. For example, optionally substituted hetero(C₅₋₁₂)aryl as used in this Application to define R⁴ includes benzofur-2-yl, fur-2-yl, fur-3-yl, pyrid-3-yl, pyrid-4-yl, quinol-2-yl, quinol-3-yl, thien-2-yl, thien-3-yl, and the like.

"Heterobicycloaryl" means bicycloaryl, as defined in this Application, provided that one or more of the ring carbon atoms indicated are replaced by a heteroatom moiety selected from -N=, -NR-, -O- or -S-, wherein R is hydrogen, (C₁₋₆)alkyl, a protecting group or represents the free valence which serves as the point of attachment to a ring nitrogen, and any carbocyclic ketone, thiketone or iminoketone derivative thereof. In general, the term heterobicycloaryl as used in this Application includes, for example, benzo[1,3]dioxol-5-ylcarbonyl, 3,4-dihydro-2H-[1,8]naphthyridinyl, 3,4-dihydro-2H-quinolinyl, 2,4-dioxo-3,4-dihydro-2H-quinazolinyl, 1,2,3,4,5,6-hexahydro[2,2']bipyridinyl, morpholinylpyridyl, 3-oxo-2,3-dihydrobenzo[1,4]oxazinyl, piperidinylphenyl, 5,6,7,8-tetrahydroquinolinyl, and the like. For example, hetero(C₈₋₁₂)bicycloaryl(C₀₋₃)alkyl used to describe R¹⁰ in this Application, includes 1-oxo-1,3-dihydroisoindol-2-yl, quinolin-3-yl, quinolin-2-yl, 3a,7a-dihydrobenzo[1,3]dioxol-5-yl, naphthalen-2-yl, 3-chlorobenzo[b]thiophen-2-yl, benzo[b]thiophen-2-yl and 1H-indol-5-yl, and the like.

"Heterocycloalkyl" means cycloalkyl, as defined in this Application, provided that one or more of the ring carbon atoms indicated are replaced by a heteroatom moiety selected from -N=, -NR-, -O- or -S-, wherein R is hydrogen, (C₁₋₆)alkyl, a protecting group or represents the free valence which serves as the point of attachment to a ring nitrogen, and any carbocyclic ketone, thiketone or iminoketone derivative thereof (e.g., the term hetero(C₅₋₁₂)cycloalkyl includes [1,4']bipiperidinyl, 1',2'-dihydro-2H-[1,4']bipyridinyl, imidazolidinyl, morpholinyl, 1-morpholin-4-ylpiperidinyl, piperazinyl, piperidyl, pyrrolidinyl, pyrrolinyl, quinuclidinyl, and the like). Thus, for

example, optionally substituted hetero(C₅-12)cycloalkyl as used in this Application to define R⁴ includes 4-*tert*-butoxycarbonylpiperazin-1-yl, 4-ethoxycarbonylpiperazin-1-yl, 4-fur-2-ylcarbonylpiperazin-1-yl, morpholin-4-yl, and the like. Suitable protecting groups include *tert*-butoxycarbonyl, benzyloxycarbonyl, 5 benzyl, 4-methoxybenzyl, 2-nitrobenzyl, and the like. For example, a compound of Formula I wherein R⁴ is piperidin-4-ylcarbonyl may exist as either the unprotected or a protected derivative, e.g., wherein R⁴ is 4-*tert*-butoxycarbonylpiperazin-1-ylcarbonyl, and both the unprotected and protected derivatives fall within the scope of the invention.

10 "Hydroxy" means the radical -OH. Unless indicated otherwise, the compounds of the invention containing hydroxy radicals include protected derivatives thereof. Suitable protecting groups for hydroxy moieties include benzyl and the like.

"Iminoketone derivative" means a derivative containing the moiety -C(NR)-, wherein R is hydrogen or (C₁₋₆)alkyl.

15 "Isomers" mean compounds of Formula I having identical molecular formulae but differ in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and stereoisomers that are nonsuperimposable mirror images 20 are termed "enantiomers" or sometimes "optical isomers". A carbon atom bonded to four nonidentical substituents is termed a "chiral center". A compound with one chiral center has two enantiomeric forms of opposite chirality is termed a "racemic mixture". A compound that has more than one chiral center has 2ⁿ⁻¹ enantiomeric pairs, where n is the number of chiral centers. Compounds with more than one chiral center may exist as 25 either an individual diastereomers or as a mixture of diastereomers, termed a "diastereomeric mixture". When one chiral center is present a stereoisomer may be characterized by the absolute configuration of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. Enantiomers are characterized by the absolute configuration of their chiral centers and 30 described by the R- and S-sequencing rules of Cahn, Ingold and Prelog. Conventions for stereochemical nomenclature, methods for the determination of stereochemistry and

the separation of stereoisomers are well known in the art (e.g., see "Advanced Organic Chemistry", 4th edition, March, Jerry, John Wiley & Sons, New York, 1992). It is understood that the names and illustration used in this Application to describe compounds of Formula I are meant to be encompassed all possible stereoisomers.

5 Thus, for example, the name *N*-{1-(Cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethane-sulfonyl]-ethyl}-nicotinamide is meant to include *N*-{(R)-1-(Cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethane-sulfonyl]-ethyl}-nicotinamide and *N*-{(S)-1-(Cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethane-sulfonyl]-ethyl}-nicotinamide and any mixture, racemic or 10 otherwise, thereof.

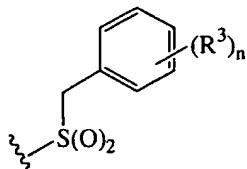
"Ketone derivative" means a derivative containing the moiety -C(O)-.

"Methylene" means the divalent radical -CH₂-.

"Nitro" means the radical -NO₂.

15 "Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, the phrase "R⁴ optionally further contains 1 to 5 substituents" means that R⁴ may or may not be substituted in order to fall within the scope of the invention.

20 "Ortho" and "meta" have the meaning typically associated with their usage in organic chemistry. Hence, the phrase "R³ at the first occurrence is attached at the ring carbon ortho or meta to the 1-position of the phenyl moiety", refers to the following illustrative example:



25 wherein R³ is attached at the 2 or 3-position.

"N-oxide derivatives" means derivatives of compounds of Formula I in which nitrogens are in an oxidized state (i.e., O-N) and which possess the desired pharmacological activity.

"Pathology" of a disease means the essential nature, causes and development of the disease as well as the structural and functional changes that result from the disease processes.

5 "Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

10 "Pharmaceutically acceptable salts" means salts of compounds of Formula I which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartatic acid, 15 citric acid, benzoic acid, *o*-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, madelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, *p*-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 20 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid and the like.

25 Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine and the like.

30 "Prodrug" means a compound which is convertible *in vivo* by metabolic means (e.g. by hydrolysis) to a compound of Formula I. For example an ester of a compound

of Formula I containing a hydroxy group may be convertible by hydrolysis in vivo to the parent molecule. Alternatively an ester of a compound of Formula I containing a carboxy group may be convertible by hydrolysis in vivo to the parent molecule.

Suitable esters of compounds of Formula I containing a hydroxy group, are for example

5 acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-*b*-hydroxynaphthoates, gentisates, isethionates, di-*p*-toluoyltartrates, methanesulphonates, ethanesulphonates, benzenesulphonates, *p*-toluenesulphonates, cyclohexylsulphamates and quinates.

Suitable esters of compounds of Formula I containing a carboxy group, are for example

10 those described by F.J.Leinweber, Drug Metab. Res., 1987, 18, page 379. An especially useful class of esters of compounds of Formula I containing a hydroxy group, may be formed from acid moieties selected from those described by Bundgaard et al., J. Med. Chem., 1989, 32, page 2503-2507, and include substituted (aminomethyl)-benzoates, for example, dialkylamino-methylbenzoates in which the two alkyl groups

15 may be joined together and/or interrupted by an oxygen atom or by an optionally substituted nitrogen atom, e.g. an alkylated nitrogen atom, more especially (morpholino-methyl)benzoates, e.g. 3- or 4-(morpholinomethyl)-benzoates, and (4-alkylpiperazin-1-yl)benzoates, e.g. 3- or 4-(4-alkylpiperazin-1-yl)benzoates.

"Protected derivatives" means derivatives of compounds of Formula I in which 20 a reactive site or sites are blocked with protecting groups. Protected derivatives of compounds of Formula I are useful in the preparation of compounds of Formula I or in themselves may be active cathepsin S inhibitors. A comprehensive list of suitable protecting groups can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

25 "Theapeutically effective amount" means that amount which, when administered to an animal for treating a disease, is sufficient to effect such treatment for the disease.

"Thioketone derivative" means a derivative containing the moiety -C(S)-.

30 "Treatment" or "treating" means any administration of a compound of the present invention and includes:

(1) preventing the disease from occurring in an animal which may be predisposed to

the disease but does not yet experience or display the pathology or symptomatology of the disease,

(2) inhibiting the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., arresting further development of the

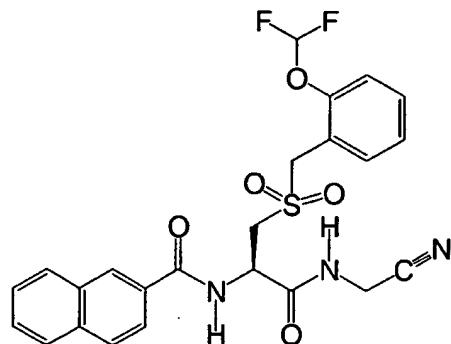
5 pathology and/or symptomatology), or

(3) ameliorating the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., reversing the pathology and/or symptomatology).

10 Nomenclature:

The compounds of Formula I and the intermediates and starting materials used in their preparation are named in accordance with IUPAC rules of nomenclature in which the characteristic groups have decreasing priority for citation as the principle group as follows: acids, esters, amides, etc. Alternatively, the compounds are named by

15 AutoNom 4.0 (Beilstein Information Systems, Inc.). For example, a compound of Formula I in which R¹ and R² are each hydrogen, R³ is difluoromethoxy in the ortho position and R⁴ is naphthalen-2-ylmethanoyl; that is, a compound having the following structure:



20

is named naphthalene-2-carboxylic acid {(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide or
N-(1*R*-cyanomethylcarbamoyl-2-(2-difluoromethoxybenzylsulfonyl)ethyl]naphthalene-
25 2-carboxamide.

Presently Preferred Embodiments:

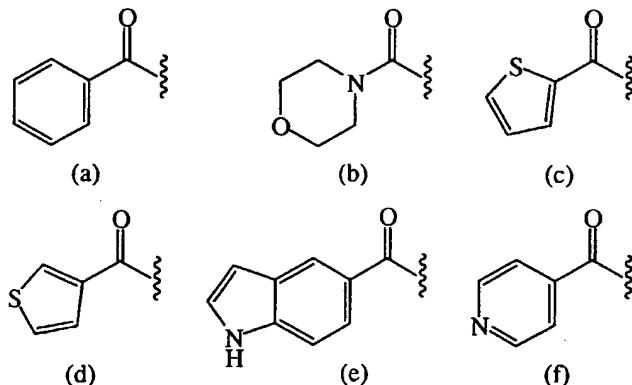
While the broadest definition of the invention is set forth in the Summary of the Invention, certain aspects of the invention are preferred. For example, R¹ particularly represents hydrogen and R² represents hydrogen, hetero(C₅)aryl or (C₁₋₄)alkyl-substituted hetero(C₅)aryl or R¹ and R² together with the carbon atom to which both R¹ and R² are attached form (C₃₋₅)cycloalkylene or (C₅₋₆)heterocycloalkylene.

Preferably n is 1 or 2 and R³ at the first occurrence is selected from a group consisting of difluoromethoxy, trifluoromethoxy, trifluorosulfanyl and nitro and R³ at the second occurrence, if present, is selected from a group consisting of (C₁₋₄)alkyl, bromo, carboxy, chloro, cyano, difluoromethoxy, fluoro, iodo, methoxy, nitro, trifluoromethoxy, trifluoromethyl and trifluorosulfanyl. Preferably R³ at the first occurrence is in the ortho or meta position.

R⁴ preferably may represent -C(O)X²R⁸ or -S(O)₂X²R⁸, wherein X² is a bond, -O- or -NR⁹-, wherein R⁹ is hydrogen or (C₁₋₆)alkyl, and R⁸ is (C₁₋₆)alkyl, (C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₀)aryl(C₀₋₃)alkyl, hetero(C₅₋₁₀)aryl(C₀₋₃)alkyl, hetero(C₈₋₁₂)bicycloaryl(C₀₋₃)alkyl, or phenyl(C₀₋₃)alkyl, wherein the phenyl is substituted by -X³OR¹² or -X³C(O)R¹², wherein X³ is a bond or methylene and R¹² is phenyl(C₀₋₃)alkyl, wherein any aryl or heteroaryl group comprising R⁴ optionally is substituted in the ring by 1 to 2 substituents selected from (C₁₋₆)alkyl, halo, halo-substituted (C₁₋₃)alkyl, -X⁴NR¹⁴R¹⁴ and -X⁴OR¹⁴, wherein X⁴ is a bond or (C₁₋₆)alkylene, R¹⁴ is hydrogen, (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl. R⁴ more preferably may represent allyloxycarbonyl, 2-aminopyridinylcarbonyl, 25 benzo[1,3]dioxolylcarbonyl, benzothienyl, benzoyl, 3-benzoylbenzoyl, 4-bromobenzoyl, 3-bromothienyl, biphenylylcarbonyl, 3-chlorobenzothienyl, 4-chlorobenzoyl, 3-chlorothienyl, cyclopentylcarbonyl, 3,4-difluorobenzoyl, dimethylcarbamoyl, 3,4-dimethoxybenzoyl, 4-fluorobenzoyl, 3-fluoro-4-hydroxybenzoyl, 2-hydroxypyridinylcarbonyl, 3-hydroxypyridinylcarbonyl, 30 indolylcarbonyl, isobutyloxycarbonyl, isopropylcarbamoyl, isopropoxycarbonyl, 4-methoxybenzoyl, methoxycarbonyl, 3-methylbenzoyl, 2-methylthienylcarbonyl,

4-methylvaleryl, morpholin-1-ylcarbonyl, naphthalenylcarbonyl, naphthalenylsulfonyl, phenoxy carbonyl, phenylacryloyl, phenylsulfonyl, pyrazinylcarbonyl, pyridinylcarbonyl, quinolyl, thienylcarbonyl, thienylsulfonyl, 4-trifluoromethoxybenzoyl or 4-trifluoromethylbenzoyl.

5 R^4 more preferably is benzoyl, indolylcarbonyl, morpholin-4-ylcarbonyl, thienylcarbonyl or pyridinylcarbonyl optionally substituted in the ring by 1 to 2 substituents selected from fluoro and methyl. In particular, R^4 represents one of the following formulae:



10

namely benzoyl, morpholin-4-ylcarbonyl, thien-2-yl, thien-3-yl and indol-4-yl, respectively, optionally substituted in the ring by 1 to 2 substituents selected from fluoro, methoxy and methyl.

15 Reference to the preferred embodiments set forth above is meant to include all combinations of particular and preferred groups.

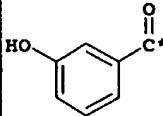
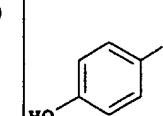
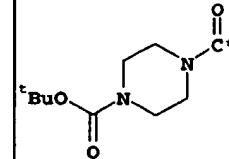
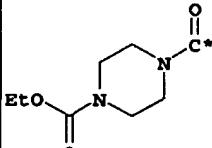
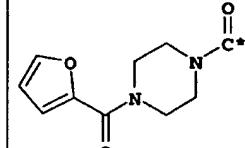
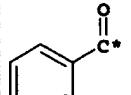
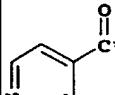
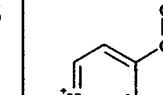
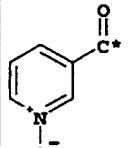
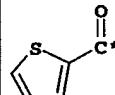
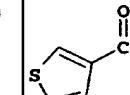
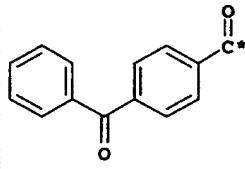
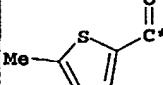
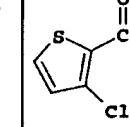
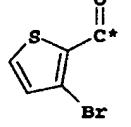
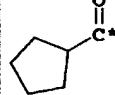
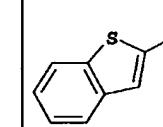
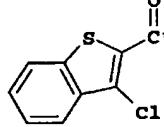
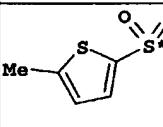
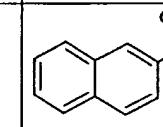
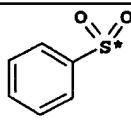
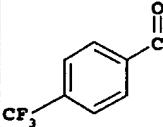
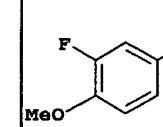
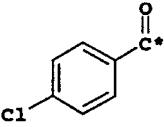
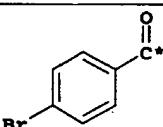
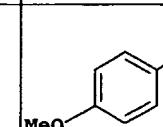
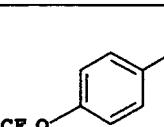
Particular compounds of the invention are selected from the compounds formed by joining the acyl carbon atom (C^*) of one of the fragments (A1 to A36 or A40 to A71) shown in Table 1 to the nitrogen atom (N^*) of one of the substituted aminoalkyl fragments (B1 to B75) shown in Table 2, and joining the methine carbon atom (CH^*) of one of the substituted aminoalkyl fragments (B1 to B75) shown in Table 2 to the acyl carbon atom (C^*) of one of the acyl-aminoalkyl nitrile fragments (C1 to C9) depicted in Table 3.

Further particular compounds of the invention are selected from the compounds

formed by joining the sulphonyl atom (SO_2^*) of one of the fragments (A37 to A39) shown in Table 1 to the nitrogen atom (N^*) of one of the substituted aminoalkyl fragments (B1 to B75) shown in Table 2, and joining the methine carbon atom (CH^*) of one of the substituted aminoalkyl fragments (B1 to B75) shown in Table 2 to the acyl carbon atom (C^*) of one of the acyl-aminoalkynitrile fragments(C1 to C9) depicted in Table 3.

TABLE 1

A1		A2		A3	
A4		A5		A6	
A7		A8		A9	
A10		A11		A12	
A13		A14		A15	
A16		A17		A18	

A19		A20		A21	
A22		A23		A24	
A25		A26		A27	
A28		A29		A30	
A31		A32		A33	
A34		A35		A36	
A37		A38		A39	
A40		A41		A42	
A43		A44		A45	

A46		A47		A48	
A49		A50		A51	
A52		A53		A54	
A55		A56		A57	
A58		A59		A60	
A61		A62		A63	
A64		A65		A66	
A67		A68		A69	
A70		A71		A72	

TABLE 2

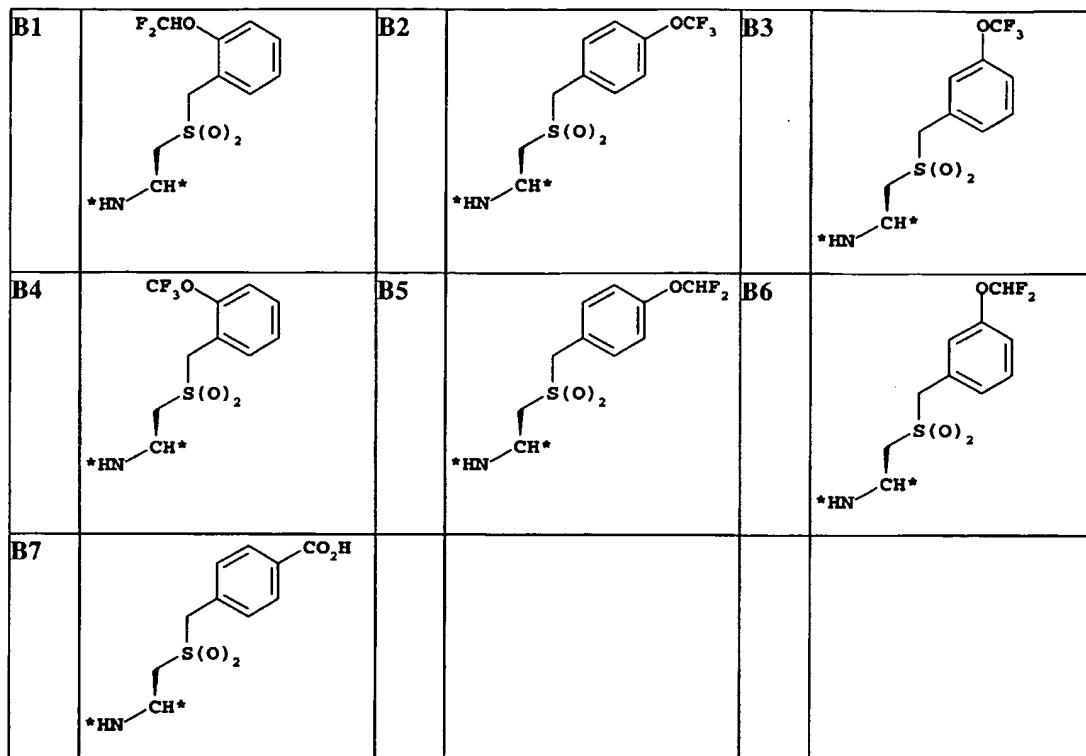
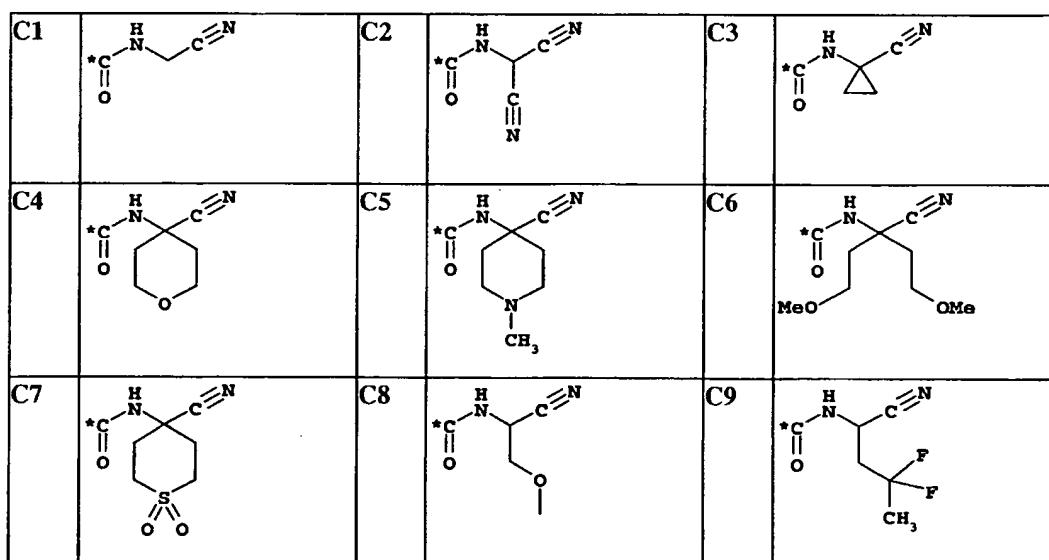


TABLE 3

5



C10					
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Particularly preferred examples of fragments "A", "B", and "C" are illustrated below:

A1-B1-C1; A1-B1-C2; A1-B1-C3; A1-B1-C4; A1-B1-C5; A1-B1-C6;
 A1-B1-C7; A1-B1-C8; A1-B1-C9; A2-B1-C1; A2-B1-C2; A2-B1-C3;
 A2-B1-C4; A2-B1-C5; A2-B1-C6; A2-B1-C7; A2-B1-C8; A2-B1-C9;
 A3-B1-C1; A3-B1-C2; A3-B1-C3; A3-B1-C4; A3-B1-C5; A3-B1-C6;
 A3-B1-C7; A3-B1-C8; A3-B1-C9; A4-B1-C1; A4-B1-C2; A4-B1-C3;
 A4-B1-C4; A4-B1-C5; A4-B1-C6; A4-B1-C7; A4-B1-C8; A4-B1-C9;
 A5-B1-C1; A5-B1-C2; A5-B1-C3; A5-B1-C4; A5-B1-C5; A5-B1-C6;
 A5-B1-C7; A5-B1-C8; A5-B1-C9; A6-B1-C1; A6-B1-C2; A6-B1-C3;
 A6-B1-C4; A6-B1-C5; A6-B1-C6; A6-B1-C7; A6-B1-C8; A6-B1-C9;
 A7-B1-C1; A7-B1-C2; A7-B1-C3; A7-B1-C4; A7-B1-C5; A7-B1-C6;
 A7-B1-C7; A7-B1-C8; A7-B1-C9; A8-B1-C1; A8-B1-C2; A8-B1-C3;
 A8-B1-C4; A8-B1-C5; A8-B1-C6; A8-B1-C7; A8-B1-C8; A8-B1-C9;
 A9-B1-C1; A9-B1-C2; A9-B1-C3; A9-B1-C4; A9-B1-C5; A9-B1-C6;
 A9-B1-C7; A9-B1-C8; A9-B1-C9; A10-B1-C1; A10-B1-C2; A10-B1-C3;
 A10-B1-C4; A10-B1-C5; A10-B1-C6; A10-B1-C7; A10-B1-C8; A10-B1-C9;
 A11-B1-C1; A11-B1-C2; A11-B1-C3; A11-B1-C4; A11-B1-C5; A11-B1-C6;
 A11-B1-C7; A11-B1-C8; A11-B1-C9; A12-B1-C1; A12-B1-C2; A12-B1-C3;
 A12-B1-C4; A12-B1-C5; A12-B1-C6; A12-B1-C7; A12-B1-C8; A12-B1-C9;
 A13-B1-C1; A13-B1-C2; A13-B1-C3; A13-B1-C4; A13-B1-C5; A13-B1-C6;
 A13-B1-C7; A13-B1-C8; A13-B1-C9; A14-B1-C1; A14-B1-C2; A14-B1-C3;
 A14-B1-C4; A14-B1-C5; A14-B1-C6; A14-B1-C7; A14-B1-C8; A14-B1-C9;
 A15-B1-C1; A15-B1-C2; A15-B1-C3; A15-B1-C4; A15-B1-C5; A15-B1-C6;
 A15-B1-C7; A15-B1-C8; A15-B1-C9; A16-B1-C1; A16-B1-C2; A16-B1-C3;
 A16-B1-C4; A16-B1-C5; A16-B1-C6; A16-B1-C7; A16-B1-C8; A16-B1-C9;
 A17-B1-C1; A17-B1-C2; A17-B1-C3; A17-B1-C4; A17-B1-C5; A17-B1-C6;
 A17-B1-C7; A17-B1-C8; A17-B1-C9; A18-B1-C1; A18-B1-C2; A18-B1-C3;
 A18-B1-C4; A18-B1-C5; A18-B1-C6; A18-B1-C7; A18-B1-C8; A18-B1-C9;
 A19-B1-C1; A19-B1-C2; A19-B1-C3; A19-B1-C4; A19-B1-C5; A19-B1-C6;
 A19-B1-C7; A19-B1-C8; A19-B1-C9; A20-B1-C1; A20-B1-C2; A20-B1-C3;
 A20-B1-C4; A20-B1-C5; A20-B1-C6; A20-B1-C7; A20-B1-C8; A20-B1-C9;
 A21-B1-C1; A21-B1-C2; A21-B1-C3; A21-B1-C4; A21-B1-C5; A21-B1-C6;
 A21-B1-C7; A21-B1-C8; A21-B1-C9; A22-B1-C1; A22-B1-C2; A22-B1-C3;
 A22-B1-C4; A22-B1-C5; A22-B1-C6; A22-B1-C7; A22-B1-C8; A22-B1-C9;
 A23-B1-C1; A23-B1-C2; A23-B1-C3; A23-B1-C4; A23-B1-C5; A23-B1-C6;
 A23-B1-C7; A23-B1-C8; A23-B1-C9; A24-B1-C1; A24-B1-C2; A24-B1-C3;
 A24-B1-C4; A24-B1-C5; A24-B1-C6; A24-B1-C7; A24-B1-C8; A24-B1-C9;

A25-B1-C1; A25-B1-C2; A25-B1-C3; A25-B1-C4; A25-B1-C5; A25-B1-C6;
A25-B1-C7; A25-B1-C8; A25-B1-C9; A26-B1-C1; A26-B1-C2; A26-B1-C3;
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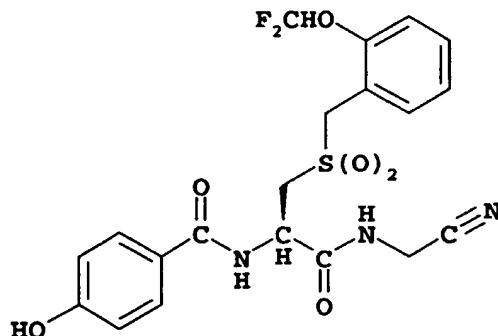
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A71-B7-C1; A71-B7-C2; A71-B7-C3; A71-B7-C4; A71-B7-C5; A71-B7-C6;
A71-B7-C7; A71-B7-C8; A71-B7-C9;

Thus, for example, in the above list the compound denoted as A20-B2-C1 is the product of the combination of group A20 in Table 1 and B2 in Table 2 and C1 in Table 3, namely *N*-(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-4-hydroxy-benzamide:

5



Further preferred are compounds of Formula I selected from a group consisting of:

10 *N*-[1R-cyanomethylcarbamoyl-2-(2-difluoromethoxybenzylsulfonyl)ethyl]-morpholine-4-carboxamide, (compound denoted as A2-B1-C1);
 thiophene-2-carboxylic acid-{(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide, (compound denoted as A28-B1-C1);

15 thiophene-3-carboxylic acid-{(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide, (compound denoted as A29-B1-C1);
N-{(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-4-fluoro-benzamide, (compound denoted as A49-B1-C1);

20 morpholine-4-carboxylic acid-{(R)-1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide, (compound denoted as A2-B1-C5);
 5-methyl-thiophene-2-carboxylic acid-{(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide, (compound denoted as

A31-B1-C1);

1H-indole-5-carboxylic acid-<{(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide, (compound denoted as A60-B1-C1);

5 *N*-{(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-3-methyl-benzamide, (compound denoted as A2-B1-C1);

10 *N*-{(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-3,4-difluoro-benzamide, (compound denoted as A46-B1-C1);

15 *N*-{(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-isonicotinamide, (compound denoted as A25-B1-C1);

N-[1R-(1-cyanocyclopropylcarbamoyl)-2-(2-difluoromethoxybenzylsulfonyl)-ethyl]morpholine-4-carboxamide, (compound denoted as A2-B1-C3); and the N-oxide

20 derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

25 **Pharmacology and Utility:**

The compounds of the invention are selective inhibitors of cathepsin S and, as such, are useful for treating diseases in which cathepsin S activity contributes to the pathology and/or symptomatology of the disease. For example, the compounds of the invention are useful in treating autoimmune disorders, including, but not limited to,

30 juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis and Hashimoto's thyroiditis, allergic disorders, including, but not limited to, asthma, and allogeneic immune responses, including, but not limited to, organ transplants or tissue grafts.

Cathepsin S also is implicated in disorders involving excessive elastolysis, such

35 as chronic obstructive pulmonary disease (e.g., emphysema), bronchiolitis, excessive airway elastolysis in asthma and bronchitis, pneumonitis and cardiovascular disease

such as plaque rupture and atheroma. Cathepsin S is implicated in fibril formation and, therefore, inhibitors of cathepsins S are of use in treatment of systemic amyloidosis.

The cysteine protease inhibitory activities of the compounds of the invention can be determined by methods known to those of ordinary skill in the art. Suitable

5 *in vitro* assays for measuring protease activity and the inhibition thereof by test compounds are known. Typically, the assay measures protease induced hydrolysis of a peptide based substrate. Details of assays for measuring protease inhibitory activity are set forth in Examples 5, 6, 7 and 8, *infra*.

10 Administration and Pharmaceutical Compositions:

In general, compounds of Formula I will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with another therapeutic agent. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative

15 health of the subject, the potency of the compound used and other factors. For example, therapeutically effective amounts of a compound of Formula I may range from about 1 micrograms per kilogram body weight ($\mu\text{g}/\text{kg}$) per day to about 1 milligram per kilogram body weight (mg/kg) per day, typically from about 10 $\mu\text{g}/\text{kg}/\text{day}$ to about 0.1 $\text{mg}/\text{kg}/\text{day}$. Therefore, a therapeutically effective amount for 20 a 80 kg human patient may range from about 100 $\mu\text{g}/\text{day}$ to about 100 mg/day , typically from about 1 $\mu\text{g}/\text{day}$ to about 10 mg/day . In general, one of ordinary skill in the art, acting in reliance upon personal knowledge and the disclosure of this Application, will be able to ascertain a therapeutically effective amount of a compound of Formula I for treating a given disease.

25 The compounds of Formula I can be administered as pharmaceutical compositions by one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous or subcutaneous). Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any 30 other appropriate composition and are comprised of, in general, a compound of

Formula I in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the active ingredient. Such excipient may be any solid, liquid, semisolid or, in the case of an aerosol composition, gaseous excipient that is generally

5 available to one of skill in the art.

Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, and the like. Liquid and semisolid excipients may be selected from water, ethanol, glycerol, propylene glycol

10 and various oils, including those of petroleum, animal, vegetable or synthetic origin (e.g., peanut oil, soybean oil, mineral oil, sesame oil, and the like). Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose and glycols.

The amount of a compound of Formula I in the composition may vary widely

15 depending upon the type of formulation, size of a unit dosage, kind of excipients and other factors known to those of skill in the art of pharmaceutical sciences. In general, a composition of a compound of Formula I for treating a given disease will comprise from 0.01%w to 10%w, preferably 0.3%w to 1%w, of active ingredient with the remainder being the excipient or excipients. Preferably the pharmaceutical composition

20 is administered in a single unit dosage form for continuous treatment or in a single unit dosage form ad libitum when relief of symptoms is specifically required.

Representative pharmaceutical formulations containing a compound of Formula I are described in Example 9.

25 Chemistry:

Processes for Making Compounds of Formula I:

Compounds of the invention may be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature, for example those described by R.C. Larock in *Comprehensive Organic*

30 *Transformations*, VCH publishers, 1989.

In the reactions described hereinafter it may be necessary to protect reactive

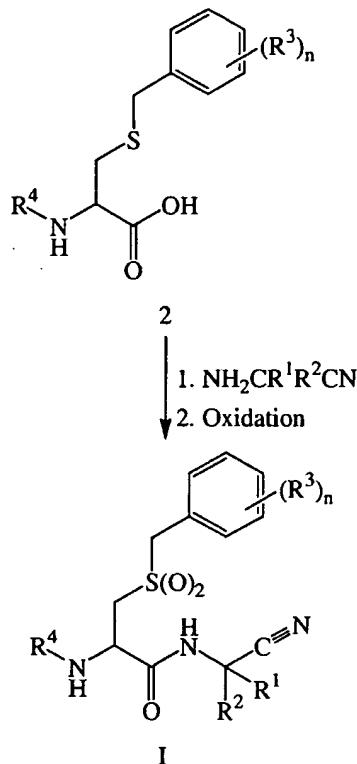
functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions.

Conventional protecting groups may be used in accordance with standard practice, for examples see T.W. Greene and P. G. M. Wuts in "Protective Groups in Organic

5 Chemistry" John Wiley and Sons, 1991.

Compounds of Formula I can be prepared by proceeding as in the following
Reaction Scheme 1:

Reaction Scheme 1



10 in which each n, R¹, R², R³ and R⁴ are as defined for Formula I in the Summary of the Invention.

Compounds of Formula I can be prepared by condensing an acid of Formula 2 with an aminoalkanonitrile of the formula NH₂CR¹R²CN and then oxidizing. The 15 condensation reaction can be effected with an appropriate coupling agent (e.g., benzotriazol-1-yloxytrispyrrolidinophosphonium hexafluorophosphate (PyBOP[®]), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI),

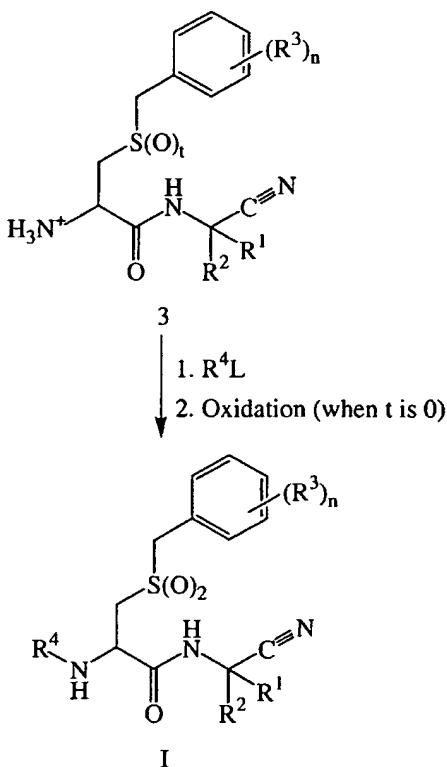
O-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU), 1,3-dicyclohexylcarbodiimide (DCC), or the like) and optionally an appropriate catalyst (e.g., 1-hydroxybenzotriazole (HOBr), 1-hydroxy-7-azabenzotriazole (HOAt), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3, tetra-methyluroniumhexafluorophosphate (HATU), 5 or the like) and non-nucleophilic base (e.g., *N*-methylpyrrolidinone, *N*-methylmorpholine, and the like, or any suitable combination thereof) at ambient temperature and requires 5 to 10 hours to complete.

The oxidation can be carried out with an oxidizing agent (e.g., Oxone[®], or the like) in a suitable solvent (e.g., methanol, water, or the like, or any suitable combination 10 thereof) at ambient temperature and requires 16 to 24 hours to complete. A detailed description for the synthesis of a compound of Formula I by the processes in Reaction Scheme 1 is set forth in the Examples 2 and 4, infra.

Compounds of Formula I can be prepared by proceeding as in the following Reaction Scheme 2:

15

Reaction Scheme 2



in which t is 0 or 2, L is a leaving group and each n, R¹, R², R³ and R⁴ are as defined for Formula I in the Summary of the Invention.

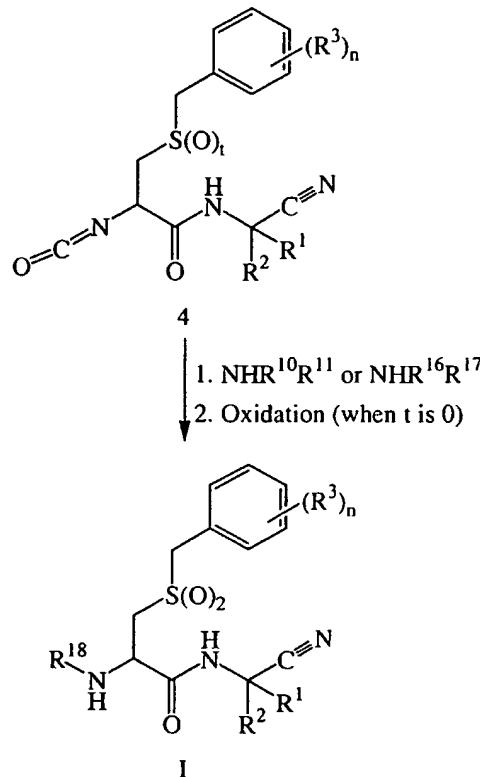
Compounds of Formula I can be prepared by condensing a compound of 5 Formula 3 with a compound of the formula R⁴L (e.g., 3-acetylbenzoic acid, nicotinic acid, morpholin-4-ylcarbonyl chloride, or the like) and then oxidizing when t is 0. When L is chloro the condensation can be carried out at ambient temperature in the presence of a suitable non-nucleophilic base (e.g., triethylamine, N-methylmorpholine, or the like) in a suitable solvent (e.g., dichloromethane, tetrahydrofuran, or the like) and 10 requires 16 to 24 hours to complete. When L is hydroxy the condensation typically is effected in the presence of a suitable coupling agent (e.g., (PyBOP[®]), EDCI, HBTU, DCC, or the like) and optionally an appropriate catalyst (e.g., 1-hydroxybenzotriazole (HOEt), 1-hydroxy-7-azabenzotriazole (HOAt), or the like) in a suitable solvent (e.g., dichloromethane, tetrahydrofuran, or the like, or any suitable combination thereof) at 15 ambient temperature and requires 16 to 24 hours to complete.

The oxidization can be carried out by the process described above for Reaction Scheme 1.

Compounds of Formula I in which R⁴ is -NR¹⁰R¹¹ or -NR¹⁶R¹⁷ can be prepared by proceeding as in the following Reaction Scheme 3:

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Reaction Scheme 3

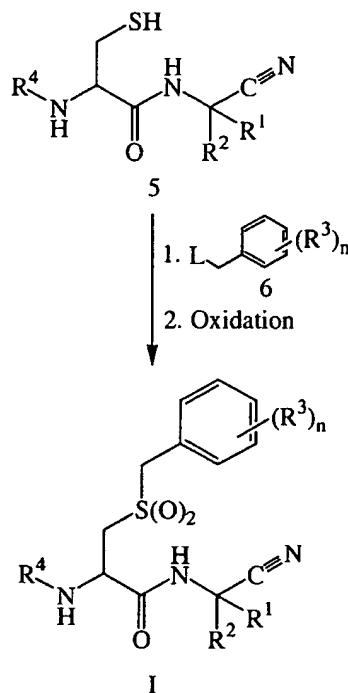


in which t is 0 or 2, R^{18} is $-\text{NR}^{10}\text{R}^{11}$ or $-\text{NR}^{16}\text{R}^{17}$, wherein R^{16} and R^{17} together with the
 5 nitrogen atom to which R^{16} and R^{17} are attached form hetero(C₅₋₁₂)cycloalkyl and each
 n , R^1 , R^2 , R^3 , R^{10} and R^{11} are as defined in the Summary of the Invention.

Compounds of Formula I in which R^4 is $-\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$ or $-\text{C}(\text{O})\text{NR}^{16}\text{R}^{17}$,
 wherein R^{16} and R^{17} together with the nitrogen atom to which R^{16} and R^{17} are attached
 form hetero(C₅₋₁₂)cycloalkyl can be prepared by condensing a compound of Formula 4
 10 with a compound of the formula $\text{NHR}^{10}\text{R}^{11}$ or $\text{NHR}^{16}\text{R}^{17}$, respectively, and then
 oxidizing when n is 0. The condensation reaction can be carried out at ambient
 temperature in a suitable solvent (e.g., dichloromethane, or the like) and requires 16 to
 24 hours to complete. The oxidation can be carried out by the process described
 above for Reaction Scheme 1.

15 Compounds of Formula I can be prepared by proceeding as in the following
 Reaction Scheme 4:

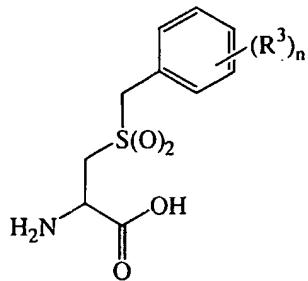
Reaction Scheme 4



5 in which L is a leaving group and each n, R¹, R², R³ and R⁴ are as defined for Formula I in the Summary of the Invention.

Compounds of Formula I can be prepared by reacting a compound of Formula 5 with a compound of Formula 6 and then oxidizing. The reaction is carried out in the presence of base (e.g., potassium hydroxide, or the like) at ambient temperature and 10 requires 2 to 3 hours to complete. The oxidation can be carried out by the process described above for Reaction Scheme 1. A detailed description for the synthesis of a compound of Formula I by the processes in Reaction Scheme 1 is set forth in the Examples 1 and 2, infra.

15 Compounds of Formula 2 can be prepared by reacting a compound of Formula 7:

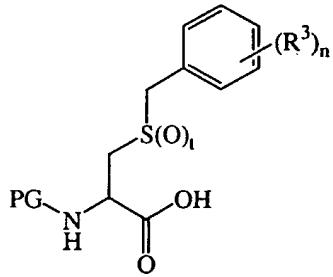


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with a compound of the formula R⁴L, in which L is a leaving group and n and R³ are as defined in the Summary of the Invention. The reaction can be carried out in the

5 presence of base (e.g., 1 N aqueous sodium hydroxide, or the like) at about 5° C. A detailed description for the synthesis of a compound of Formula 2 is set forth in the References, infra. Alternatively, compounds of Formula 7 are commercially available or otherwise can be prepared by methods known in the art or analogous to those described elsewhere in this Application. A detailed description for the synthesis of a 10 compound of Formula 7 by the process described above is set forth in the Reference 1, infra.

Compounds of Formula 3 can be prepared by condensing a compound of Formula 8:



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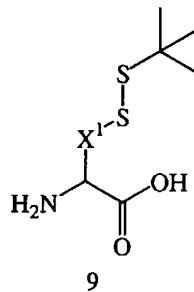
with an aminoalkanonitrile of the formula NH₂CR¹R²CN, in which PG is a protecting group and each n, R¹, R² and R³ are as defined in the Summary of the Invention, optionally oxidizing and then deprotecting. The condensation reaction can be effected with an appropriate condensing agent (e.g., N,N-dicyclohexylidimide,

20 diisopropylcarbodiimide, carbonyldiimidazole, or the like) and a suitable

non-nucleophilic base (e.g., *N*-methylpyrrolidinone, *N*-methylmorpholine, or the like, or any suitable combination thereof) in a suitable solvent (e.g., dichloromethane, or the like) at ambient temperature and requires 2 to 3 days to complete. Oxidation can be carried out by the process described above for Reaction Scheme 1. Deprotection can be effected by any means which removes the protective group and gives the desired product in reasonable yield. A detailed description of the techniques applicable to the creation of protective groups and their removal can be found in T.W. Greene, *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999. A convenient method of deprotecting is by treatment with a suitable acid (e.g., *p*-toluenesulfonic acid, or the like) providing the acid addition salt in the process.

Compounds of Formula 4 can be prepared by reacting a compound of Formula 3 with phosgene. The reaction is carried out conveniently in a biphasic solvent (e.g., an equal mixture of dichloromethane and saturated sodium bicarbonate solution at ambient temperature.

Compounds of Formula 5 can be prepared by sequentially condensing an acid of Formula 9:



with an aminoalkanonitrile of the formula $\text{NHR}^2\text{CR}^3\text{R}^4\text{CN}$ and a compound of the formula R^4L and then deprotecting. The condensation reaction with the aminoalkanonitrile is carried out in a fashion analogous to the process described above for the preparation of the compounds of Formula 3. The condensation reaction with the compound of the formula R^4L is carried out in a fashion analogous to the process described above for the preparation of the compounds of Formula I by Scheme 2. The deprotection can be effected by treatment with a suitable reducing agent (e.g., tris-butyl phosphine, tris-carboxyethyl phosphine, or the like) in the presence of base (e.g.,

aqueous potassium hydroxide, or the like) in a suitable solvent (e.g., DMF, or the like) under an inert atmosphere and at ambient temperature and requires 12 to 24 hours. A detailed description for the synthesis of a compound of Formula 5 by the processes described above is set forth in the Reference 2, infra.

5

Additional Processes for Preparing Compounds of Formula I:

A compound of Formula I can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a compound of Formula I can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Inorganic and organic acids and bases suitable for the preparation of the pharmaceutically acceptable salts of compounds of Formula I are set forth in the definitions section of this Application. Alternatively, the salt forms of the compounds of Formula I can be prepared using salts of the starting materials or intermediates.

The free acid or free base forms of the compounds of Formula I can be prepared from the corresponding base addition salt or acid addition salt form. For example, a compound of Formula I in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, and the like). A compound of Formula I in a base addition salt form can be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc.).

The *N*-oxides of compounds of Formula I can be prepared by methods known to those of ordinary skill in the art. For example, *N*-oxides can be prepared by treating an unoxidized form of the compound of Formula I with an oxidizing agent (e.g., trifluoroperacetic acid, permaleic acid, perbenzoic acid, peracetic acid, *meta*-chloroperoxybenzoic acid, or the like) in a suitable inert organic solvent (e.g., a halogenated hydrocarbon such as dichloromethane) at approximately 0°C. Alternatively, the *N*-oxides of the compounds of Formula I can be prepared from the *N*-oxide of an appropriate starting material.

Compounds of Formula I in unoxidized form can be prepared from *N*-oxides of compounds of Formula I by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in an suitable inert organic solvent (e.g., acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80°C.

5 Prodrug derivatives of the compounds of Formula I can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier *et al.*(1994), *Bioorganic and Medicinal Chemistry Letters*, Vol. 4, p. 1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound of
10 Formula I with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbonochloridate, *para*-nitrophenyl carbonate, or the like).

Protected derivatives of the compounds of Formula I can be made by means known to those of ordinary skill in the art. A detailed description of the techniques applicable to the creation of protecting groups and their removal can be found in T.W.

15 Greene, *Protecting Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1981.

Compounds of the present invention may be conveniently prepared, or formed during the process of the invention, as solvates (e.g. hydrates). Hydrates of compounds of the present invention may be conveniently prepared by recrystallisation from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran
20 or methanol.

Compounds of Formula I can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomer. While resolution of enantiomers can be
25 carried out using covalent diastereomeric derivatives of compounds of Formula I, dissociable complexes are preferred (e.g., crystalline diastereoisomeric salts).

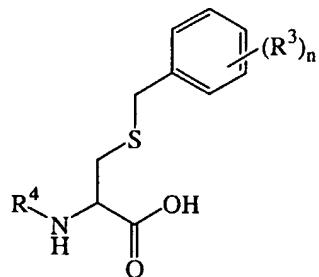
Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography or, preferably,
30 by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical

means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques Andre Collet, Samuel H. Wilen, *Enantiomers, Racemates and Resolutions*, John Wiley & Sons, Inc. (1981).

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In summary, the compounds of Formula I are made by a process which comprises:

(A) reacting a compound of Formula 2:

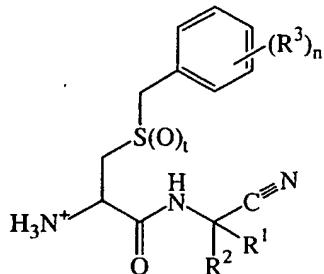


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with a compound of the formula $\text{NH}_2\text{CR}^1\text{R}^2\text{CN}$, in which n , R^1 , R^2 , R^3 and R^4 are as defined in the Summary of the Invention for Formula I; or

(B) reacting a compound of Formula 3:

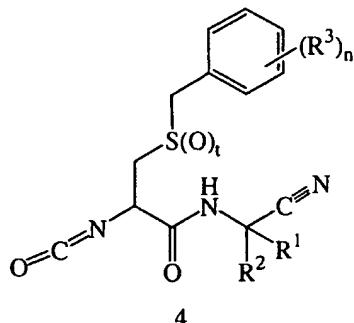


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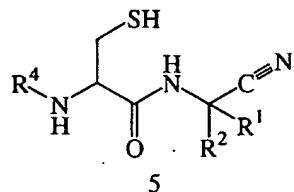
with a compound of the formula R^4L , in which t is 0 or 2, L is a leaving group and each n , R^1 , R^2 , R^3 and R^4 are as defined in the Summary of the Invention for Formula I, and then oxidizing when t is 0; or

20 (C) reacting a compound of Formula 4:



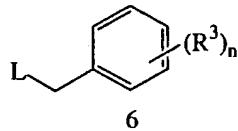
with a compound of formula $\text{NHR}^{10}\text{R}^{11}$ or $\text{NHR}^{16}\text{R}^{17}$ to provide a compound of
 Formula I in which R^4 is $-\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$ or $-\text{C}(\text{O})\text{NR}^{16}\text{R}^{17}$, respectively, wherein t is 0 or
 5 2, R^{16} and R^{17} together with the nitrogen atom to which R^{16} and R^{17} are attached form
 hetero(C_{5-12})cycloalkyl and each n , R^1 , R^2 , R^3 , R^{10} and R^{11} are as defined in the
 Summary of the Invention for Formula I, and then oxidizing when t is 0; or

(D) reacting a compound of Formula 5:



10

with a compound of Formula 6:



15 in which L is a leaving group and each X^1 , X^2 , R^1 , R^2 , R^3 and R^4 are as defined in the
 Summary of the Invention for Formula I; and

(E) optionally converting a compound of Formula I into a pharmaceutically acceptable

salt;

(F) optionally converting a salt form of a compound of Formula I to non-salt form;

(G) optionally converting an unoxidized form of a compound of Formula I into a

20 pharmaceutically acceptable *N*-oxide;

(H) optionally converting an *N*-oxide form of a compound of Formula I its unoxidized

form;

(I) optionally resolving an individual isomer of a compound of Formula I from a mixture of isomers;

(J) optionally converting a non-derivatized compound of Formula I into a pharmaceutically prodrug derivative; and

5 (K) optionally converting a prodrug derivative of a compound of Formula I to its non-derivatized form.

Examples:

The present invention is further exemplified, but not limited by, the following 10 examples that illustrate the preparation of compounds of Formula I (Examples) and intermediates (References) according to the invention.

REFERENCE 1

(R)-3-[2-(1,1-Difluoro-methoxy)-phenylmethanesulfonyl]-2-[(1-morpholin-4-yl-methanoyl)-amino]-propionic acid

A solution of *(R)*-2-*tert*-butoxycarbonylamino-3-((*R*)-2-*tert*-butoxycarbonylamino-2-carboxy-ethyldisulfanyl)-propionic acid (i.e., Boc-L-Cystine) (25 g, 56.75 mmol) in DMF (250 mL) was treated with 20 tris(carboxyethyl)phosphine hydrochloride (17.9 g, 62.4 mmol). A solution of KOH (31.8 g, 567 mmol) in water (100 mL) was added over 2 minutes and the exothermic reaction was cooled with a 20°C water bath. The mixture was stirred for 2 hours at room temperature, diluted with 2-(difluoromethoxy)benzyl bromide and stirred for 2 hours. The mixture was acidified with 1N HCl and extracted with ethyl acetate (3 x 250mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was dried under high vacuum and then dissolved in CH_2Cl_2 (80 mL). The solution was diluted with trifluoroacetic acid (80 mL) and the mixture was stirred at room temperature for 2.5 hours. All volatile components were removed under vacuum and the residue was dissolved in water (200 mL). The solution was 25 adjusted to pH 6 to 7 with 1N NaOH to give a precipitate, which was collected by filtration, washed with water and dried under vacuum to yield (*R*)-2-amino-

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3-[2-(1,1-difluoro-methoxy)-benzylsulfanyl]-propionic acid as white solid (27.5 g).

A mixture of (*R*)-2-amino-3-[2-(1,1-difluoro-methoxy)-benzylsulfanyl]-propionic acid (5 g, 18.03 mmol) and *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (8.5 mL, 45.8 mmol) was heated at 70°C under N₂ for 1 hour. All volatile reaction products were removed under vacuum. The residue was dissolved in CH₂Cl₂ (10 mL) and the solution treated with morpholinecarbonyl chloride (4.2 mL, 36 mmol). The mixture was stirred at room temperature for 16 hours and then diluted with ethyl acetate (300mL). The mixture was washed with water (50 mL) and brine (100 mL), dried (MgSO₄) and concentrated. The residue was dissolved in methanol (250 mL) and a saturated aqueous solution of Oxone® (35 g, 57 mmol) was added. The mixture was stirred at room temperature for 2 hours. The methanol was removed under vacuum and the remaining aqueous phase was extracted with ethyl acetate (3 x 200mL). The combined organic layers were washed with brine, dried (MgSO₄) and evaporated. The product was purified by flash chromatography on silica gel (Eluent: ethyl acetate to 10% methanol in ethyl acetate) to yield (*R*)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-[(1-morpholin-4-yl-methanoyl)-amino]-propionic acid as colorless oil (6.5 g).

REFERENCE 2

20 *N*-[2-*tert*-Butyldisulfanyl-1*R*-cyanomethylcarbamoylethyl]morpholine-4-carboxamide

A solution comprised of 2*R*-amino-3-*tert*-butyldisulfanylpropionic acid hydrate (25 g, 119 mmol) in sodium hydroxide (1N, 300 mL) was cooled to 0°C and then treated with 4-morpholinecarbonyl chloride (13.9 mL, 119 mmol) added slowly.

25 The mixture was treated with additional amounts of sodium hydroxide (5N, 100 mL) and 4-morpholinecarbonyl chloride (27.8 mL, 238 mmol), stirred for approximately 12 hours and acidification with concentrated hydrochloric acid. Product was extracted with ethyl acetate and the combined extracts were washed with brine, dried (MgSO₄) and concentrated. The product was recrystallized from ethyl acetate/hexane, to provide 30 3-*tert*-butyldisulfanyl-2*R*-morpholin-4-ylcarbonylaminopropionic acid (16.5 g, 51.2 mmol) as a white crystalline solid.

A suspension of 3-*tert*-butyldisulfanyl-2*R*-morpholin-4-ylcarbonylaminopropionic acid (16.25 g, 50.4 mmol) in methylene chloride (100 mL) was treated with EDCI (10.6 g, 55.4 mmol), HOBr (8.85 g, 65.5 mmol) and aminoacetonitrile hydrochloride (7.0 g, 75.6 mmol). The mixture then was treated with 5 4-methylmorpholine (8.31 mL, 75.6 mmol), stirred at ambient temperature for 5 hours and then diluted with ethyl acetate (500 mL). The dilution was washed with saturated aqueous sodium bicarbonate solution, brine, 1N hydrochloric acid and brine, dried (MgSO₄) and concentrated. Product was purified from the residue by flash chromatography on silica gel with ethyl acetate as eluent to provide *N*-[2-*tert*-butyldisulfanyl-1*R*-cyanomethylcarbamoylethyl]morpholine-4-carboxamide (7.5 g) as a 10 white solid.

The following intermediate was provided by proceeding as in Reference 2:
N-[2-*tert*-butyldisulfanyl-1*R*-cyanomethylcarbamoylethyl]morpholine-15 4-carboxamide.

REFERENCE 3

2-(2-thienyl)aminoacetonitrile hydrochloride

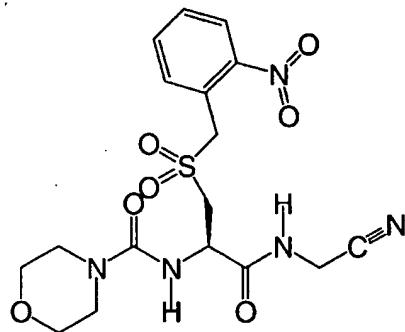
20 A mixture of ammonium chloride (24.9g, 465 mmol) and 2-thiophenecarboxaldehyde (21.2 mL, 227mmol) in 250mL diethyl ether was treated with an 80mL aqueous solution of sodium cyanide (16.7g, 341 mmol) over 20 minutes. The mixture was allowed to stir for 16 hours. The aqueous layer was removed. The ether layer was washed (2 x 100mL) with saturation sodium bicarbonate solution, dried over 25 anhydrous magnesium sulfate, and concentrated. The residue was dissolved in 250 mL diethyl ether and cooled in an ice bath. Hydrogen chloride was bubbled through the solution until precipitation was complete. The salt was filtered and dried under reduced pressure to give 9.8g of 2-(2-thienyl)aminoacetonitrile hydrochloride.

30 The following intermediate was provided by proceeding as in reference 3:
Amino-furan-2-yl-acetonitrile

EXAMPLE 1

*N-[1*R*-Cyanomethylcarbamoyl-2-(2-nitrobenzylsulfonyl)ethyl]morpholine-4-carboxamide*

5 (Compound 1)



A mixture comprised of *N*-(2-*tert*-butyldisulfanyl-1*R*-cyanomethylcarbamoyl-

10 ethyl)morpholine-4-carboxamide (560 mg, 1.6 mmol), provided as in Reference 2, tris-carboxyethyl phosphine (550 mg, 1.9 mmol) and DMF (4.5 mL) was treated with 4M aqueous potassium hydroxide (2 mL) with stirring at 23° C. The mixture was stirred for 3 hours under a nitrogen atmosphere and then treated with 2-nitrobenzyl bromide (830 mg, 3.8 mmol). The mixture was stirred for 16 hours and then diluted 15 with ethyl acetate (200 mL). The organic phase was separated, sequentially washed with brine, saturated sodium bicarbonate and brine, dried (MgSO_4) and concentrated under reduced pressure. The residue was dissolved in 1:1 ethyl acetate/hexane and product was crystallized from solution to provide *N*-[1*R*-cyanomethylcarbamoyl-2-(2-nitrobenzylsulfonyl)ethyl]morpholine-4-carboxamide (478 mg) as a colorless 20 solid. Mass Spectrum: m/e 399.2 (theory 398). NMR Spectrum (DMSO- d_6) δ 8.79 (t, J = 5.1 Hz, 1H), 8.69 (d, J = 8.1 Hz, 1H), 7.97 (d, J = 8.1 Hz, 1H), 7.86 (d, J = 8.4 Hz, 2H), 7.58 - 7.65 (m, 2H), 7.43-7.55 (m, 4H), 4.62 (ddd, J = 13.6, 9.2, 5.1 Hz, 1H), 4.12 (d, J = 5.5 Hz, 2H), 4.06 (d, J = 3.0 Hz, 2H), 2.87 (dd, J = 13.5, 5.1, 1H), 2.76 (dd, J = 13.6, 9.5 Hz, 1H).

25 A solution comprised of *N*-[1*R*-cyanomethylcarbamoyl-2-(2-

nitrobenzylsulfanyl)-ethyl]morpholine-4-carboxamide (50 mg, 0.13 mmol) in methanol (5 mL) was treated with Oxone® (105 g, 0.17 mmol) in water (1 mL) and the reaction mixture was stirred at 25° C for 16 hours. The reaction mixture then was diluted with cold water and the product was extracted with ethyl acetate. The extracts were dried

5 and concentrated. The residue was dissolved in ethyl acetate and product was crystallized from solution to provide N-[1R-cyanomethylcarbamoyl-2-(2-nitrobenzylsulfonyl)ethyl]morpholine-4-carboxamide (45 g, 0.1 mmol). Mass Spectrum: m/e 431 (theory 430). NMR Spectrum (DMSO-d₆) δ 8.99 (d, 1H, J = 8.1 Hz), 8.83 (t, J = 5.1 Hz, 1H), 8.05 (d, J = 8.1 Hz, 1H), 7.86 (d, J = 8.1 Hz, 2H), 7.76 (d, 10 J = 7 Hz, 1H), 7.64-7.69 (m, 2H), 7.46 - 7.61 (m, 3H), 5.08 (s, 2H), 5.03 (t, J = 6.6 Hz, 1H), 4.13 (s, 2H), 3.83 (d, J = 14.3 Hz, 1H), 3.66 (dd, J = 14.3, 9.9 Hz, 1H).

The following compounds of Formula I were provided by proceeding as in Example 1:

15 N-[1R-cyanomethylcarbamoyl-2-(4-trifluoromethoxybenzylsulfonyl)ethyl]benzamide (Compound 2); EI MS (M+ = 470.2); NMR (DMSO): δ 9.00 (d, 1H, J = 8.24 Hz), 8.82 (t, 1H, J = 5.6 Hz), 7.89 (d, 2H, J = 9.7 Hz), 7.40 - 7.58 (m, 7H), 5.04 - 5.11 (m, 1H), 4.65 (s, 2H), 4.15 (s, 1H), 3.82 (dd, 1H, J = 14.3, 3.2Hz), 3.59 (dd, 1H, J = 12.0, 9.7 Hz);

20 N-[1R-cyanomethylcarbamoyl-2-(4-trifluoromethylsulfanylbenzylsulfonyl)ethyl]benzamide (Compound 3); EI MS (M+ = 486.2); NMR (DMSO): δ 9.02 (d, 1H, J = 7.9 Hz), 8.82 (t, 1H, J = 5.7 Hz), 7.89 (d, 2H, J = 8.4 Hz), 7.76 (d, 2H, J = 8.2 Hz), 7.47 - 7.61 (m, 5H), 5.07 (t, 1H, J = 9.4 Hz), 4.70 (s, 2H), 4.15 (d, 2H, J = 5.7 Hz), 3.84 (dd, 1H, J = 14.6, 3.5 Hz), 3.61 (dd, 1H, J = 14.1, 94. Hz);

25 N-[1R-cyanomethylcarbamoyl-2-(3-nitrobenzylsulfonyl)ethyl]benzamide (Compound 4); EI MS (M+ = 431.0); NMR (DMSO): δ 8.99 (d, 1H, J = 8.0 Hz), 8.82 (t, 1H, J = 5.7 Hz), 8.32 (s, 1H), 8.27 (d, 1H, J = 8.2 Hz), 7.88 (m, 3H), 7.73 (t, 1H, J = 3.1 Hz), 7.47 - 7.60 (m, 3H), 5.06 (t, 1H, J = 11.1 Hz), 4.82 (s, 2H), 4.14 (s, 2H), 3.86 (dd, 1H, J = 14.4, 3.2 Hz), 3.62 (dd, 1H, J = 14.6, 9.4 Hz);

N-[1*R*-cyanomethylcarbamoyl-2-(4-nitrobenzylsulfonyl)ethyl]benzamide

(Compound 5); NMR (DMSO): δ 8.98 (d, 1H, J = 7.7 Hz), 8.80 (t, 1H, J = 4.8 Hz), 8.25 (d, 2H, J = 6.6 Hz), 7.86 (d, 2H, J = 7.0 Hz), 7.67 (d, 2H, J = 7.0 Hz), 7.45 - 7.58 (m, 3H), 5.04 (t, 1H, 7.7 Hz), 4.80 (s, 2H), 4.12 (s, 2H), 3.84 (d, 1H, J = 16.8 Hz), 3.60 (dd, 1H, J = 13.6, 9.5 Hz);

N-[1*R*-cyanomethylcarbamoyl-2-(2-nitrobenzylsulfonyl)ethyl]benzamide

(Compound 6); EI MS (M^+ = 431.2), Theory = 430; NMR (DMSO): δ 8.99 (d, 1H, J = 8.1 Hz), 8.83 (t, 1H, J = 5.1 Hz), 8.05 (d, 1H, J = 8.1 Hz), 7.86 (d, 2H, J = 8.1 Hz), 7.76 (d, 1H, J = 7.0 Hz), 7.64 - 7.69 (m, 2H), 7.46 - 7.61 (m, 3H), 5.08 (s, 2H), 5.03 (t, 1H, J = 6.6 Hz), 4.13 (s, 2H), 3.83 (d, 1H, J = 14.3 Hz), 3.66 (dd, 1H, J = 14.3, 9.9 Hz);

N-[1*R*-cyanomethylcarbamoyl-2-(3-trifluoromethoxybenzylsulfonyl)ethyl]benzamide (Compound 7); EI MS (M^+ = 470.0), Theory = 469; NMR (DMSO): δ 9.00 (d, 1H, J = 8.1 Hz), 8.81 (t, 1H, J = 5.9 Hz), 7.87 (d, 2H, J = 7.3 Hz), 7.40 - 7.56 (m, 7H), 5.05 (t, 1H, J = 5.9 Hz), 4.67 (s, 2H), 4.13 (d, 2H, J = 5.5 Hz), 3.81 (d, 1H, J = 14.3 Hz), 3.57 (dd, 1H, J = 14.3, 9.9 Hz);

N-[1*R*-cyanomethylcarbamoyl-2-(2-difluoromethoxybenzylsulfonyl)ethyl]benzamide (Compound 8); Mass Spectrum: (M+H⁺) 452; (M-H⁺) 450; ¹H-NMR: (DMSO, δ) 8.99 (d, J = 8.2 Hz, 1H), 8.82 (t, J = 5.5 Hz, 1H), 7.89 (d, J = 8.2 Hz, 2H), 7.60 - 7.44 (m, 5H), 7.29 (t, J = 5.5 Hz, 1H), 7.26 (t, J = 5.5 Hz, 1H) 7.13 (t, $J_{H,F}$ = 74 Hz, 1H) 5.08 (m, 1H), 4.61 (s, 2H), 4.14 (m, 2H), 3.80 (dd, J = 2.7 Hz, J = 14.4 Hz, 1H), 3.76 (dd, J = 9.7 Hz, J = 14.4 Hz, 1H);

N-[1*R*-cyanomethylcarbamoyl-2-(2-fluoro-6-nitrobenzylsulfonyl)ethyl]benzamide (Compound 9); Mass Spectrum: (M+H⁺) 449; (M-H⁺) 447; ¹H NMR: (DMSO) 9.01 (d, J = 8.2 Hz, 1H), 8.87 (t, J = 5.4 Hz, 1H), 7.97 - 7.46 (m, 8H), 5.11-5.03 (m, 3H), 4.15 (m, 2H), 3.93 (dd, J = 3.4 Hz, J = 14.3 Hz, 1H), 3.80 (dd, J = 9.7 Hz, J = 14.5 Hz, 1H);

N-[1*R*-cyanomethylcarbamoyl-2-(3-trifluoromethylsulfanylbenzylsulfonyl)ethyl]benzamide (Compound 10); Mass

Spectrum: (M+H⁺) 486; (M-H⁺) 484; ¹H-NMR: (DMSO, δ) 9.00 (d, J = 8.2 Hz, 1H), 8.80 (t, J = 5.4Hz, 1H), 7.90 - 7.46 (m, 9H), 5.05 (m, 1H), 4.70 (s, 2H), 4.13 (m, 2H), 3.82 (dd, J = 3.2 Hz, J = 14.9 Hz, 1H), 3.58 (dd, J = 9.7 Hz, J = 14.6 Hz, 1H);

N-[1*R*-cyanomethylcarbamoyl-2-(2-

5 trifluoromethylsulfanylbenzylsulfonyl)ethyl]-benzamide (Compound 11); Mass Spectrum: (M+H⁺) 486; (M-H⁺) 484; ¹H-NMR: (DMSO, δ) 9.04 (d, J = 8.2 Hz, 1H), 8.87 (t, J = 5.6Hz, 1H), 7.92 - 7.46 (m, 9H), 5.11 (m, 1H), 4.92 (s, 2H), 4.15 (m, 2H), 3.90 (dd, J = 3.5 Hz, J = 14.8 Hz, 1H), 3.77 (dd, J = 9.7 Hz, J = 14.6 Hz, 1H);

N-[1*R*-cyanomethylcarbamoyl-2-(2-

10 trifluoromethoxybenzylsulfonyl)ethyl]benzamide (Compound 12); Mass Spectrum: (M+H⁺) 470; (M-H⁺) 468; ¹H-NMR: (DMSO, δ) 9.01 (d, J = 7.9 Hz, 1H), 8.84 (t, J = 5.3Hz, 1H), 7.89 (d, J = 7.7 Hz, 2H) 7.60 - 7.40 (m, 7H), 5.10 (m, 1H), 4.67 (s, 2H), 4.14 (m, 2H), 3.86 (dd, J = 3.2 Hz, J = 14.4 Hz, 1H), 3.70 (dd, J = 9.9 Hz, J = 14.4 Hz, 1H);

15 N-{(R)-1-(Cyanomethyl-carbamoyl)-2-[4-(1,1-difluoro-methoxy)-phenylmethane-sulfonyl]-ethyl}-benzamide (Compound 13); Mass Spectrum: (M+H⁺) 452; (M-H⁺) 450; ¹H NMR: (DMSO) 8.99 (d, J=8.2Hz, 1H), 8.80 (t, J=5.4Hz, 1H), 7.88 (m, 2H), 7.60-7.42 (m, 5H), 7.27 (t, J_{H,F}=74Hz, 1H), 7.20 (d, J=8.4Hz, 2H), 5.05 (m, 1H), 4.58 (s, 2H), 4.14 (m, 2H), 3.79 (dd, J=3.2Hz, J=14.3Hz, 1H), 3.55 (dd, , 20 J=9.5Hz, J=14.5Hz, 1H);

N-(1*R*-cyanomethylcarbamoyl-2-(3-

difluoromethoxybenzylsulfonyl)ethyl]benzamide (Compound 14); Mass Spectrum: (M+H⁺) 452; (M-H⁺) 450; ¹H-NMR: (DMSO, δ) 8.99 (d, J = 8.2 Hz, 1H), 8.81 (t, J = 6.2Hz, 1H), 7.87 (d, J = 8.2 Hz, 2H), 7.60 - 7.18 (m, 7H), 7.22 (t, J_{H,F}= 74 Hz, 1H), 25 5.05 (m, 1H), 4.62 (s, 2H), 4.14 (m, 2H), 3.81 (dd, J = 2.7 Hz, J = 14.5 Hz, 1H), 3.57 (dd, J = 9.7 Hz, J = 14.4 Hz, 1H); and

30 4-(2*R*-benzoylamino-2-cyanomethylcarbamoylethylsulfonylmethyl)benzoic acid (Compound 15); Mass Spectrum: (M+H⁺) 430; (M-H⁺) 428; ¹H NMR: (DMSO) 8.98 (d, J=8.2Hz, 1H), 8.81 (t, J=5.6Hz, 1H), 7.95 (d, J=8.2Hz, 2H), 7.88 (m, 2H), 7.60-7.46 (m, 5H), 5.06 (m, 1H), 4.69 (s, 2H), 4.13 (m, 2H), 3.81 (dd, J=3.2Hz, J=14.3Hz, 1H),

3.57 (dd, , $J=9.5\text{Hz}$, $J=14.5\text{Hz}$, 1H).

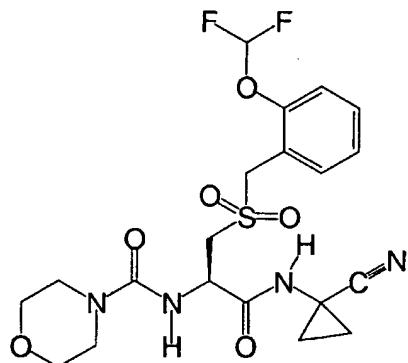
EXAMPLE 2

N-[1R-(1-cyanocyclopropylcarbamoyl)-2-(2-difluoromethoxybenzylsulfonyl)ethyl]-

5

morpholine-4-carboxamide

(Compound 16)

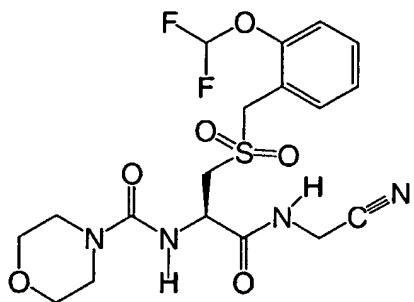


10 A mixture of (*R*)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-
 2-[(1-morpholin-4-yl-methanoyl)-amino]-propionic acid (200 mg, 0.473 mmol),
 prepared as in Reference 1, in CH_2Cl_2 (3 mL), HATU (270 mg, 0.71 mmol) and HOAt
 (64.3 mg, 0.473 mmol) was treated with 1-amino-cyclopropanecarbonitrile (116 mg,
 0.71 mmol) and N-methylmorpholine (0.156 mL, 1.42 mmol) and then DMF (3 mL) to
 15 obtain a homogenous solution. The mixture was stirred at room temperature for
 16 hours, diluted with ethyl acetate (150 mL), washed with saturated aqueous NaHCO_3
 and then brine, dried (MgSO_4) and concentrated to provide *N-[1R-(1-*
cyanocyclopropylcarbamoyl)-2-(2-difluoromethoxybenzylsulfonyl)ethyl]-morpholine-4-
carboxamide. The product was purified by flash chromatography. ^1H NMR: (DMSO)
 20 8.99 (s, 1H), 7.50-7.23 (m, 4H), 7.13 (t, $J_{\text{H},\text{F}}=74\text{Hz}$, 1H), 7.03 (d, $J=8.4\text{Hz}$, 1H), 4.64
 (m, 1H), 4.55 (s, 2H), 3.64-3.24 (m, 10H), 1.47 (m, 2H), 1.14 (m, 2H).

EXAMPLE 3

N-[1*R*-cyanomethylcarbamoyl-2-(2-difluoromethoxybenzylsulfonyl)ethyl]morpholine-4-carboxamide

5 (Compound 17)

A solution of *N*-[2-*tert*-butyldisulfanyl-1*R*-

10 cyanomethylcarbamoylethyl]morpholine-4-carboxamide (7.37 g, 20.4 mmol), provided as in Reference 2, in DMF (80 mL) was treated sequentially with tris(carboxyethyl)phosphine hydrochloride (7.03 g, 24.53 mmol) and aqueous potassium hydroxide solution (5N, 20 mL). The mixture was stirred for 5 hours and then treated with 2-difluoromethoxybenzyl bromide (14.54 g, 61.3 mmol). The mixture was stirred for 3 hours and then acidified with 1N hydrochloric acid. Product was extracted with ethyl acetate (3x150 mL) and the combined extracts were washed with brine, dried (MgSO_4) and concentrated. The residue was dissolved in methanol (500 mL) and then a saturated aqueous solution of Oxone[®] (200 mL) was added in one portion. The mixture was stirred for 2 hours and then concentrated under vacuum.

15 Product was extracted from the residue with ethyl acetate (3x150 mL). The combined extracts were washed with brine, dried (MgSO_4) and concentrated. Crude product was crystallized from ethyl acetate/hexane to provide *N*-[1*R*-cyanomethylcarbamoyl-2-(2-difluoromethoxybenzylsulfonyl)ethyl]morpholine-4-carboxamide (5.45 g) as a white crystalline solid. Mass Spectrum: ($\text{M}+\text{H}^+$) 461; ($\text{M}-\text{H}^+$) 459. $^1\text{H-NMR}$: (DMSO, δ)

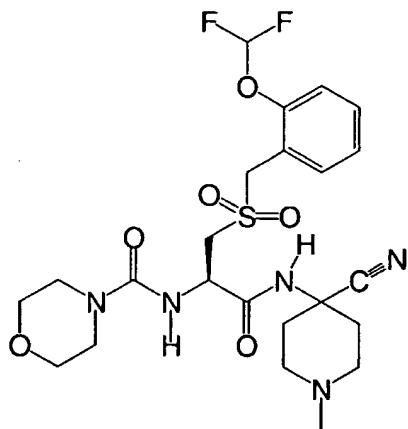
20 8.69 (t, J = 5.4 Hz, 1H), 7.54 - 7.09 (m, 4H), 7.14 (t, $J_{\text{H},\text{F}}$ = 74 Hz, 1H), 4.73 (m, 1H),

25 8.69 (t, J = 5.4 Hz, 1H), 7.54 - 7.09 (m, 4H), 7.14 (t, $J_{\text{H},\text{F}}$ = 74 Hz, 1H), 4.73 (m, 1H),

4.56 (s, 2H), 4.13 (s, 2H), 3.68 - 3.25 (m, 10H).

EXAMPLE 4

5 Morpholine-4-carboxylic acid {(R)-1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide
 (Compound 18)



A solution of (R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-

10 2-[(1-morpholin-4-yl-methanoyl)-amino]-propionic acid (200 mg, 0.473 mmol), provided as in Reference 1, in CH_2Cl_2 (3 mL) was combined with HATU (270 mg, 0.71 mmol), HOAt (64.3 mg, 0.473 mmol), 4-amino-1-methyl-piperidine-4-carbonitrile (98 mg, 0.71 mmol), N-methylmorpholine (0.156 mL, 1.42 mmol) and then DMF (3 mL) to obtain a homogenous solution. The mixture was stirred at room temperature
 15 for 16 hours, diluted with ethyl acetate (150 mL), washed with saturated aqueous NaHCO_3 and then brine, dried (MgSO_4) and concentrated. The product was purified from the residue by flash chromatography to provide morpholine-4-carboxylic acid {(R)-1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide. ^1H NMR: (DMSO) 8.62 (s, 1H), 7.51-7.23 (m, 4H), 7.13 (t, $J_{\text{H,F}}=74\text{Hz}$, 1H), 7.06 (d, $J=8.6\text{Hz}$, 1H), 4.70 (m, 1H), 4.57 (s, 2H), 3.57-3.25 (m, 10H), 2.62-1.82 (m, 11H).

The following compounds of Formula I are provided by the methods described

in this Application:

N-{(R)-1-(Cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethane-sulfonyl]-ethyl}-1-oxy-nicotinamide (Compound 19); ^1H NMR: (DMSO) 9.32 (d, $J=8.2\text{Hz}$, 1H), 8.91 (t, $J=5.6\text{Hz}$, 1H), 8.62 (s, 1H), 8.39 (d, $J=6.4\text{Hz}$, 1H), 7.70 (d, $J=8.2\text{Hz}$, 1H), 7.58-7.44 (m, 3H), 7.32-7.24 (m, 2H), 7.14 (t, $J_{\text{H},\text{F}}=74\text{Hz}$, 1H), 5.05 (m, 1H), 4.62 (s, 2H), 4.16 (m, 2H), 3.83 (dd, $J=3.0\text{Hz}$, $J=14.5\text{Hz}$, 1H), 3.58 (dd, $J=10.0\text{Hz}$, $J=14.5\text{Hz}$, 1H). MS: (M^++1) 469;

N-{(R)-1-(Cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethane-sulfonyl]-ethyl}-nicotinamide (Compound 20); ^1H NMR: (DMSO) 9.21 (d, $J=7.9\text{ Hz}$, 1H), 9.03 (s, 1H), 8.88 (t, $J=5.4\text{Hz}$, 1H), 8.73 (dd, $J=1.5\text{Hz}$, $J=4.7\text{Hz}$, 1H), 8.20 (m, 1H), 7.57-7.44 (m, 3H), 7.32-7.23 (m, 2H), 7.13 (t, $J_{\text{H},\text{F}}=74\text{Hz}$, 1H), 5.10 (m, 1H), 4.62 (s, 2H), 4.15 (m, 2H), 3.84 (dd, $J=3.0\text{Hz}$, $J=14.5\text{Hz}$, 1H), 3.62 (dd, $J=10.0\text{Hz}$, $J=14.5\text{Hz}$, 1H). MS: (M^++1) 453;

N-{(R)-1-(Cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethane-sulfonyl]-ethyl}-isonicotinamide (Compound 21); ^1H NMR: (DMSO) 9.31 (d, $J=8.4\text{ Hz}$, 1H), 8.90 (t, $J=5.4\text{Hz}$, 1H), 8.77-8.75 (m, 2H), 8.78-8.76 (m, 2H), 7.52-7.44 (m, 2H), 7.32-7.23 (m, 2H), 7.14 (t, $J_{\text{H},\text{F}}=74\text{Hz}$, 1H), 5.09 (m, 1H), 4.62 (s, 2H), 4.15 (m, 2H), 3.83 (dd, $J=3.0\text{Hz}$, $J=14.5\text{Hz}$, 1H), 3.63 (dd, $J=10.0\text{Hz}$, $J=14.5\text{Hz}$, 1H). MS: (M^++1) 453;

N-{(R)-1-(Cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-1-oxy-isonicotinamide (Compound 22); ^1H NMR: (DMSO) 9.25 (d, $J=8.2\text{ Hz}$, 1H), 8.90 (t, $J=5.4\text{Hz}$, 1H), 8.35 (d, $J=7.2\text{Hz}$, 2H), 7.82 (d, $J=7.2\text{Hz}$, 2H), 7.52-7.44 (m, 2H), 7.32-7.23 (m, 2H), 7.13 (t, $J_{\text{H},\text{F}}=74\text{Hz}$, 1H), 5.05 (m, 1H), 4.61 (s, 2H), 4.15 (m, 2H), 3.82 (dd, $J=3.0\text{Hz}$, $J=14.5\text{Hz}$, 1H), 3.60 (dd, $J=10.0\text{Hz}$, $J=14.5\text{Hz}$, 1H). MS: (M^++1) 469;

Pyridine-2-carboxylic acid {(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide (Compound 23); ^1H NMR: (DMSO) 9.34 (d, $J=8.8\text{ Hz}$, 1H), 8.78 (t, $J=5.4\text{Hz}$, 1H), 8.68 (d, $J=4.7\text{Hz}$, 1H), 8.09-7.99 (m, 2H), 7.64 (t, $J=6.2\text{Hz}$, 1H), 7.49-7.43 (m, 2H), 7.30-7.22 (m, 2H), 7.10 (t, $J_{\text{H},\text{F}}=74\text{Hz}$, 1H), 5.13 (m, 1H), 4.58 (s, 2H), 4.12 (m, 2H), 3.93-3.77 (m, 2H). MS: (M^++1) 453;

Pyrazine-2-carboxylic acid {(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide (Compound 24); ¹H NMR: (DMSO)

9.46 (d, J=8.7 Hz, 1H), 9.22 (d, J=1.5Hz, 1H), 8.91 (d, J=2.5Hz, 1H), 8.82-8.77 (m, 2H), 7.51-7.43 (m, 2H), 7.31-7.21 (m, 2H), 7.11 (t, J_{H,F}=74Hz, 1H), 5.16 (m, 1H), 4.58

5 (s, 2H), 4.13 (m, 2H), 3.91-3.78 (m, 2H). MS: (M⁺+1) 454;

N-{(R)-1-(Cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethane-sulfonyl]-ethyl}-2-hydroxy-nicotinamide (Compound 25); ¹H NMR:

(DMSO) 10.38 (d, J=7.8Hz, 1H), 8.88 (t, J=5.4Hz, 1H), 8.32 (dd, J=1.5Hz, J=7.2Hz, 1H), 7.74 (m, 1H), 7.53-7.44 (m, 2H), 7.32-7.23 (m, 2H), 7.11 (t, J_{H,F}=74Hz, 1H), 6.49

10 (t, J=6.6Hz, 1H), 5.07 (m, 1H), 4.59 (s, 2H), 4.13 (m, 2H), 3.73 (d, J=6.4Hz, 2H). MS: (M⁺+1) 469;

N-{(R)-1-(Cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethane-sulfonyl]-ethyl}-6-hydroxy-nicotinamide (Compound 26); ¹H NMR:

(DMSO) 12.03 (s, 1H), 8.83-8.77 (m, 2H), 8.01 (d, J=2.2Hz, 1H), 7.84 (dd, J=2.5Hz, J=9.4Hz, 1H), 7.52-7.44 (m, 2H), 7.32-7.23 (m, 2H), 7.13 (t, J_{H,F}=74Hz, 1H), 6.38 (d, J=9.6Hz, 1H), 4.99 (m, 1H), 4.59 (s, 2H), 4.13 (m, 2H), 3.78 (dd, J=3.0Hz, J=14.5Hz, 1H), 3.55 (dd, J=10.0Hz, J=14.5Hz, 1H). MS: (M⁺+1) 469;

2-Amino-N-{(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenyl-methanesulfonyl]-ethyl}-nicotinamide (Compound 27); ¹H NMR: (DMSO)

20 8.91 (d, J=7.9Hz, 1H), 8.82 (t, J=5.4Hz, 1H), 8.10 (d, J=3.7Hz, 1H), 7.94 (d, J=7.7Hz, 1H), 7.52-7.44 (m, 2H), 7.32-7.23 (m, 2H), 7.13 (t, J_{H,F}=74Hz, 1H), 7.05 (s, 2H), 6.61 (dd, J=4.7Hz, J=7.4Hz, 1H), 5.03 (m, 1H), 4.60 (s, 2H), 4.13 (m, 2H), 3.80 (dd, J=3.0Hz, J=14.5Hz, 1H), 3.62 (dd, J=10.0Hz, J=14.5Hz, 1H). MS: (M⁺+1) 468;

6-Amino-N-{(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-nicotinamide (Compound 28); ¹H NMR: (DMSO) 8.76

(t, J=5.4Hz, 1H), 8.66 (d, J=8.4Hz, 1H), 8.48 (s, 1H), 7.81 (d, J=8.5Hz, 1H), 7.52-7.44 (m, 2H), 7.32-7.23 (m, 2H), 7.12 (t, J_{H,F}=74Hz, 1H), 6.56 (s, 2H), 6.43 (d, J=8.7Hz, 1H), 5.02 (m, 1H), 4.58 (s, 2H), 4.12 (m, 2H), 3.77 (dd, J=3.0Hz, J=14.5Hz, 1H), 3.61 (dd, J=10.0Hz, J=14.5Hz, 1H). MS: (M⁺+1) 468;

30 3-Hydroxy-pyridine-2-carboxylic acid {(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide (Compound 29); ¹H

NMR: (DMSO) 12.04 (s, 1H), 9.64 (d, J=9.2Hz, 1H), 8.84 (t, J=5.4Hz, 1H), 8.20 (d, J=4.5Hz, 1H), 7.57 (dd, J=4.5Hz, J=8.7Hz, 1H), 7.52-7.44 (m, 3H), 7.31-7.22 (m, 2H), 7.11 (t, J_{H,F}=74Hz, 1H), 5.15 (m, 1H), 4.60 (s, 2H), 4.14 (m, 2H), 3.94-3.81 (m, 2H).

MS: (M⁺+1) 469;

5 Morpholine-4-carboxylic acid {(R)-1-(4-cyano-tetrahydro-pyran-4-ylcarbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide

(Compound 30); ¹H NMR: (DMSO) 8.75 (s, 1H), 7.51-7.44 (m, 2H), 7.32-7.23 (m, 2H), 7.13 (t, J_{H,F}=74Hz, 1H), 7.04 (d, J=8.4Hz, 1H), 4.72 (m, 1H), 4.57 (s, 2H), 3.78 (m, 2H), 3.60-3.25 (m, 12H), 2.24-2.10 (m, 2H), 1.98-1.84 (m, 2H). MS: (M⁺+1) 531;

10 (R)-N-Cyanomethyl-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-(3-pyridin-3-yl-ureido)-propionamide (Compound 31); ¹H NMR: (DMSO) 9.08 (s, 1H),

8.90 (t, J=5.4Hz, 1H), 8.55 (d, J=2.5Hz, 1H), 8.14 (dd, J=1.2Hz, J=4.7Hz, 1H), 7.90 (m, 1H), 7.52-7.44 (m, 2H), 7.32-7.23 (m, 3H), 7.14 (t, J_{H,F}=74Hz, 1H), 6.84 (d, J=8.9Hz, 1H), 4.84 (m, 1H), 4.61 (s, 2H), 4.15 (m, 2H), 3.70 (dd, J=4.2Hz, J=14.5Hz, 1H), 3.60 (dd, J=8.4Hz, J=14.5Hz, 1H). MS: (M⁺+1) 468;

(R)-N-Cyanomethyl-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-(3-pyridin-4-yl-ureido)-propionamide (Compound 32); ¹H NMR: (DMSO) 9.34 (s, 1H),

8.92 (t, J=5.4Hz, 1H), 8.31 (d, J=5.9Hz, 2H), 7.52-7.37 (m, 4H), 7.32-7.23 (m, 2H), 7.14 (t, J_{H,F}=74Hz, 1H), 6.92 (d, J=8.4Hz, 1H), 4.84 (m, 1H), 4.61 (s, 2H), 4.15 (m,

20 2H), 3.71 (dd, J=4.2Hz, J=14.5Hz, 1H), 3.61 (dd, J=8.4Hz, J=14.5Hz, 1H). MS: (M⁺+1) 468;

(R)-N-Cyanomethyl-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-(3-isopropyl-ureido)-propionamide (Compound 33); ¹H NMR: (DMSO) 8.76 (t, J=5.4Hz,

1H), 7.52-7.44 (m, 2H), 7.32-7.23 (m, 2H), 7.13 (t, J_{H,F}=74Hz, 1H), 6.31 (d, J=8.7Hz, 1H), 6.15 (d, J=7.7Hz, 1H), 4.71 (m, 1H), 4.55 (s, 2H), 4.12 (m, 2H), 3.75-3.40 (m, 3H), 1.03 (d, J=6.4Hz, 6H). MS: (M⁺+1) 433;

(R)-N-Cyanomethyl-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-(3,3-dimethyl-ureido)-propionamide (Compound 34); ¹H NMR: (DMSO) 8.65 (t,

J=5.4Hz, 1H), 7.52-7.44 (m, 2H), 7.32-7.23 (m, 2H), 7.13 (t, J_{H,F}=74Hz, 1H), 6.84 (d, J=7.0Hz, 1H), 4.71 (m, 1H), 4.55 (s, 2H); 4.11 (m, 2H), 3.68-3.51 (m, 2H), 2.82 (s, 6H). MS: (M⁺+1) 419;

{(R)-1-(Cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethane-sulfonyl]-ethyl}-carbamic acid methyl ester (Compound 35); ^1H NMR: (DMSO) 8.87 (t, $J=5.4\text{Hz}$, 1H), 7.75 (d, $J=8.6\text{Hz}$, 1H), 7.52-7.44 (m, 2H), 7.32-7.23 (m, 2H), 7.14 (t, $J_{\text{H},\text{F}}=74\text{Hz}$, 1H), 4.62 (m, 1H), 4.57 (s, 2H), 4.12 (m, 2H), 3.66 (dd, $J=3.2\text{Hz}$, $J=14.5\text{Hz}$, 1H), 3.57 (s, 3H), 3.42 (dd, $J=9.4\text{Hz}$, $J=14.5\text{Hz}$, 1H). MS: (M^++1) 406;

{(R)-1-(Cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethane-sulfonyl]-ethyl}-carbamic acid allyl ester (Compound 36); ^1H NMR: (DMSO) 8.87 (t, $J=5.4\text{Hz}$, 1H), 7.84 (d, $J=8.6\text{Hz}$, 1H), 7.52-7.44 (m, 2H), 7.32-7.23 (m, 2H), 7.14 (t, $J_{\text{H},\text{F}}=74\text{Hz}$, 1H), 5.90 (m, 1H), 5.31 (d, $J=17\text{Hz}$, 1H), 5.18 (d, $J=10.6\text{Hz}$, 1H), 4.62 (m, 1H), 4.57 (s, 2H), 4.51 (m, 2H), 4.12 (m, 2H), 3.66 (dd, $J=3.2\text{Hz}$, $J=14.5\text{Hz}$, 1H), 3.44 (dd, $J=9.4\text{Hz}$, $J=14.5\text{Hz}$, 1H). MS: (M^++1) 432;

{(R)-1-(Cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethane-sulfonyl]-ethyl}-carbamic acid isopropyl ester (Compound 37); ^1H NMR: (DMSO) 8.80 (t, $J=5.4\text{Hz}$, 1H), 7.60 (d, $J=8.4\text{Hz}$, 1H), 7.52-7.44 (m, 2H), 7.32-7.23 (m, 2H), 7.14 (t, $J_{\text{H},\text{F}}=74\text{Hz}$, 1H), 4.77 (sept, $J=6.4\text{Hz}$, 1H), 4.62 (m, 1H), 4.56 (s, 2H), 4.13 (m, 2H), 3.64 (dd, $J=3.2\text{Hz}$, $J=14.5\text{Hz}$, 1H), 3.43 (dd, $J=9.4\text{Hz}$, $J=14.5\text{Hz}$, 1H), 1.19 (d, $J=6.4\text{Hz}$, 3H), 1.16 (d, $J=6.4\text{Hz}$, 3H). MS: (M^++1) 434;

{(R)-1-(Cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethane-sulfonyl]-ethyl}-carbamic acid isobutyl ester (Compound 38); ^1H NMR: (DMSO) 8.82 (t, $J=5.4\text{Hz}$, 1H), 7.71 (d, $J=8.7\text{Hz}$, 1H), 7.52-7.44 (m, 2H), 7.32-7.23 (m, 2H), 7.14 (t, $J_{\text{H},\text{F}}=74\text{Hz}$, 1H), 4.61 (m, 1H), 4.56 (s, 2H), 4.13 (m, 2H), 3.86-3.69 (m, 2H), 3.65 (dd, $J=3.4\text{Hz}$, $J=14.5\text{Hz}$, 1H), 3.44 (dd, $J=9.6\text{Hz}$, $J=14.5\text{Hz}$, 1H), 1.84 (sept, $J=6.4\text{Hz}$, 1H), 0.88 (d, $J=6.6\text{Hz}$, 6H). MS: (M^++1) 448;

N-{(R)-1-(Cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethane-sulfonyl]-ethyl}-3,4-difluoro-benzamide (Compound 39); ^1H NMR: (DMSO) 9.12 (d, $J=8.2\text{Hz}$, 1H), 8.87 (t, $J=5.4\text{Hz}$, 1H), 7.90 (m, 1H), 7.76 (m, 1H), 7.65-7.44 (m, 3H), 7.32-7.23 (m, 2H), 7.13 (t, $J_{\text{H},\text{F}}=74\text{Hz}$, 1H), 5.06 (m, 1H), 4.61 (s, 2H), 4.14 (m, 2H), 3.82 (dd, $J=3.2\text{Hz}$, $J=14.5\text{Hz}$, 1H), 3.61 (dd, $J=10.0\text{Hz}$, $J=14.5\text{Hz}$, 1H). MS: (M^++1) 488;

N-{(R)-1-(Cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethane-sulfonyl]-ethyl}-3,4-dimethoxy-benzamide (Compound 40); ^1H NMR:

(DMSO) 8.86 (d, J=8.2Hz, 1H), 8.80 (t, J=5.4Hz, 1H), 7.54-7.44 (m, 4H), 7.32-7.23 (m, 2H), 7.12 (t, J_{H,F}=74Hz, 1H), 7.05 (d, J=8.4Hz, 1H), 5.05 (m, 1H), 4.59 (s, 2H), 4.13 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.79 (dd, J=3.2Hz, J=14.5Hz, 1H), 3.64 (dd, J=10.0Hz, J=14.5Hz, 1H). MS: (M⁺+1) 512;

5 N-[(R)-1-(Cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethane-sulfonyl]-ethyl]-3-methyl-benzamide (Compound 41); ¹H NMR: (DMSO) 8.94 (d, J=8.2Hz, 1H), 8.80 (t, J=5.4Hz, 1H), 7.71-7.64 (m, 2H), 7.52-7.23 (m, 6H), 7.13 (t, J_{H,F}=74Hz, 1H), 5.07 (m, 1H), 4.60 (s, 2H), 4.13 (m, 2H), 3.81 (dd, J=3.2Hz, J=14.5Hz, 1H), 3.65 (dd, J=10.0Hz, J=14.5Hz, 1H), 2.37 (s, 3H). MS: (M⁺+1)

10 466;

Thiophene-3-carboxylic acid [(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl]-amide (Compound 42); ¹H NMR: (DMSO) 8.86 (d, J=8.2Hz, 1H), 8.84 (t, J=5.4Hz, 1H), 8.18 (dd, J=1.0Hz, J=2.7Hz, 1H), 7.61 (dd, J=2.9Hz, J=4.9Hz, 1H), 7.53-7.44 (m, 3H), 7.32-7.23 (m, 2H), 7.12 (t, J_{H,F}=74Hz, 1H), 5.02 (m, 1H), 4.59 (s, 2H), 4.13 (m, 2H), 3.79 (dd, J=3.2Hz, J=14.5Hz, 1H), 3.60 (dd, J=10.0Hz, J=14.5Hz, 1H). MS: (M⁺+1) 458;

15 N-[(R)-1-(Cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethane-sulfonyl]-ethyl]-4-fluoro-benzamide (Compound 43); ¹H NMR: (DMSO) 9.03 (d, J=8.2Hz, 1H), 8.84 (t, J=5.4Hz, 1H), 7.97-7.92 (m, 2H), 7.53-7.23 (m, 6H), 7.13 (t, J_{H,F}=74Hz, 1H), 5.07 (m, 1H), 4.61 (s, 2H), 4.14 (m, 2H), 3.81 (dd, J=3.2Hz, J=14.5Hz, 1H), 3.64 (dd, J=10.0Hz, J=14.5Hz, 1H). MS: (M⁺+1) 470;

20 4-Methyl-pentanoic acid [(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl]-amide (Compound 44); ¹H NMR: (DMSO) 8.73 (t, J=5.4Hz, 1H), 8.41 (d, J=8.4Hz, 1H), 7.53-7.44 (m, 2H), 7.32-7.23 (m, 2H), 7.14 (t, J_{H,F}=74Hz, 1H), 4.83 (m, 1H), 4.56 (s, 2H), 4.12 (m, 2H), 3.67 (dd, J=3.9Hz, J=14.5Hz, 1H), 3.39 (dd, J=9.0Hz, J=14.5Hz, 1H), 2.14 (t, J=7.4Hz, 2H), 1.58-1.35 (m, 3H), 0.84 (d, J=6.4Hz, 6H). MS: (M⁺+1) 446;

25 Thiophene-2-carboxylic acid [(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl]-amide (Compound 45); ¹H NMR: (DMSO) 9.02 (d, J=8.2Hz, 1H), 8.87 (t, J=5.4Hz, 1H), 7.80 (m, 2H), 7.53-7.44 (m, 2H), 7.32-7.23 (m, 2H), 7.18 (dd, J=3.9Hz, J=4.9Hz, 1H), 7.12 (t, J_{H,F}=74Hz, 1H), 5.02

(m, 1H), 4.60 (s, 2H), 4.14 (m, 2H), 3.80 (dd, J=3.2Hz, J=14.5Hz, 1H), 3.61 (dd, J=10.0Hz, J=14.5Hz, 1H). MS: (M⁺+1) 458;

5 4-Bromo-N-{(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenyl-methanesulfonyl]-ethyl}-benzamide (Compound 46); ¹H NMR: (DMSO) 9.08 (d, J=8.2Hz, 1H), 8.84 (t, J=5.4Hz, 1H), 7.82 (d, J=8.7Hz, 2H), 7.72 (d, J=8.7Hz, 2H), 7.53-7.44 (m, 2H), 7.32-7.23 (m, 2H), 7.13 (t, J_{H,F}=74Hz, 1H), 5.06 (m, 1H), 4.60 (s, 2H), 4.14 (m, 2H), 3.81 (dd, J=3.2Hz, J=14.5Hz, 1H), 3.62 (dd, J=10.0Hz, J=14.5Hz, 1H). MS: (M⁺+1) 530, 532;

10 N-{(R)-1-(Cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethane-sulfonyl]-ethyl}-4-methoxy-benzamide (Compound 47); ¹H NMR: (DMSO) 8.83 (d, J=8.2Hz, 1H), 8.78 (t, J=5.4Hz, 1H), 7.86 (d, J=8.6Hz, 2H), 7.52-7.44 (m, 2H), 7.32-7.23 (m, 2H), 7.12 (t, J_{H,F}=74Hz, 1H), 7.02 (d, J=8.7Hz, 2H), 5.05 (m, 1H), 4.59 (s, 2H), 4.13 (m, 2H), 3.81 (s, 3H), 3.79 (dd, J=3.2Hz, J=14.5Hz, 1H), 3.64 (dd, J=10.0Hz, J=14.5Hz, 1H). MS: (M⁺+1) 482;

15 N-{(R)-1-(Cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethane-sulfonyl]-ethyl}-4-trifluoromethoxy-benzamide (Compound 48); ¹H NMR: (DMSO) 9.12 (d, J=8.2Hz, 1H), 8.85 (t, J=5.4Hz, 1H), 8.00 (d, J=8.6Hz, 2H), 7.54-7.44 (m, 4H), 7.32-7.23 (m, 2H), 7.13 (t, J_{H,F}=74Hz, 1H), 5.08 (m, 1H), 4.61 (s, 2H), 4.14 (m, 2H), 3.82 (dd, J=3.2Hz, J=14.5Hz, 1H), 3.63 (dd, J=10.0Hz, J=14.5Hz, 1H). MS: (M⁺+1) 536;

20 Naphthalene-2-carboxylic acid {(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide (Compound 49); ¹H NMR: (DMSO) 9.18 (d, J=8.2Hz, 1H), 8.87 (t, J=5.4Hz, 1H), 8.49 (s, 1H), 8.05-7.94 (m, 4H), 7.66-7.57 (m, 2H), 7.53-7.44 (m, 2H), 7.32-7.23 (m, 2H), 7.13 (t, J_{H,F}=74Hz, 1H), 5.14 (m, 1H), 4.63 (s, 2H), 4.16 (m, 2H), 3.85 (dd, J=3.2Hz, J=14.5Hz, 1H), 3.69 (dd, J=10.0Hz, J=14.5Hz, 1H). MS: (M⁺+1) 502;

25 (E)-N-{(R)-1-(Cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethane-sulfonyl]-ethyl}-3-phenyl-acrylamide (Compound 50); ¹H NMR: (DMSO) 8.88 (t, J=5.4Hz, 1H), 8.78 (d, J=8.2Hz, 1H), 7.61-7.38 (m, 8H), 7.32-7.23 (m, 2H), 7.14 (t, J_{H,F}=74Hz, 1H), 6.66 (d, J=16Hz, 1H), 4.99 (m, 1H), 4.60 (s, 2H), 4.14 (m, 2H), 3.75 (dd, J=3.2Hz, J=14.5Hz, 1H), 3.49 (dd, J=10.0Hz, J=14.5Hz, 1H). MS:

(M⁺+1) 478;

5-Methyl-thiophene-2-carboxylic acid {(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide (Compound 51); ¹H NMR: (DMSO) 8.87 (d, J=8.2Hz, 1H), 8.84 (t, J=5.4Hz, 1H), 7.59 (d, J=3.7Hz, 1H), 7.52-7.44 (m, 2H), 7.32-7.23 (m, 2H), 7.12 (t, J_{H,F}=74Hz, 1H), 6.86 (m, 1H), 4.99 (m, 1H), 4.58 (s, 2H), 4.13 (m, 2H), 3.78 (dd, J=3.4Hz, J=14.5Hz, 1H), 3.63 (dd, J=10.0Hz, J=14.5Hz, 1H), 2.47 (s, 3H). MS: (M⁺+1) 472;

Biphenyl-4-carboxylic acid {(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide (Compound 52); ¹H NMR: (DMSO) 9.06 (d, J=8.4Hz, 1H), 8.86 (t, J=5.4Hz, 1H), 7.98 (d, J=8.4Hz, 2H), 7.81 (d, J=8.4Hz, 2H), 7.74 (d, J=7.4Hz, 2H), 7.53-7.38 (m, 5H), 7.32-7.23 (m, 2H), 7.14 (t, J_{H,F}=74Hz, 1H), 5.11 (m, 1H), 4.61 (s, 2H), 4.15 (m, 2H), 3.83 (dd, J=3.2Hz, J=14.5Hz, 1H), 3.68 (dd, J=10.0Hz, J=14.5Hz, 1H). MS: (M⁺+1) 528;

1H-Indole-5-carboxylic acid {(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide; (Compound 53); ¹H NMR: (DMSO) 11.36 (s, 1H), 8.83 (d, J=8.2Hz, 1H), 8.78 (t, J=5.4Hz, 1H), 8.18 (s, 1H), 7.66 (dd, J=1.7Hz, J=8.4Hz, 1H), 7.53-7.42 (m, 4H), 7.32-7.23 (m, 2H), 7.12 (t, J_{H,F}=74Hz, 1H), 6.55 (m, 1H), 5.10 (m, 1H), 4.60 (s, 2H), 4.14 (m, 2H), 3.80 (dd, J=3.5Hz, J=14.5Hz, 1H), 3.70 (dd, J=9.2Hz, J=14.5Hz, 1H). MS: (M⁺+1) 491;

Benzo[1,3]dioxole-5-carboxylic acid {(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide (Compound 54); ¹H NMR: (DMSO) 8.83 (d, J=8.2Hz, 1H), 8.79 (t, J=5.4Hz, 1H), 7.52-7.39 (m, 4H), 7.32-7.23 (m, 2H), 7.13 (t, J_{H,F}=74Hz, 1H), 7.02 (d, J=8.2Hz, 1H), 6.10 (s, 2H), 5.03 (m, 1H), 4.59 (s, 2H), 4.13 (m, 2H), 3.78 (dd, J=3.2Hz, J=14.5Hz, 1H), 3.62 (dd, J=10.0Hz, J=14.5Hz, 1H). MS: (M⁺+1) 496;

Benzo[b]thiophene-2-carboxylic acid {(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide (Compound 55); ¹H NMR: (DMSO) 9.30 (d, J=8.2Hz, 1H), 8.92 (t, J=5.4Hz, 1H), 8.12 (s, 1H), 8.06-7.97 (m, 2H), 7.53-7.40 (m, 4H), 7.32-7.23 (m, 2H), 7.13 (t, J_{H,F}=74Hz, 1H), 5.07 (m, 1H), 4.62 (s, 2H), 4.16 (m, 2H), 3.83 (dd, J=3.2Hz, J=14.5Hz, 1H), 3.63 (dd, J=10.0Hz, J=14.5Hz, 1H). MS: (M⁺+1) 508;

N-(*R*)-1-(Cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethane-sulfonyl]-ethyl}-3-phenoxy-benzamide (Compound 56); ^1H NMR: (DMSO) 9.04 (d, $J=8.2\text{Hz}$, 1H), 8.82 (t, $J=5.4\text{Hz}$, 1H), 7.66 (d, $J=8.2\text{Hz}$, 1H), 7.55-7.37 (m, 6H), 7.32-7.14 (m, 4H), 7.12 (t, $J_{\text{H},\text{F}}=74\text{Hz}$, 1H), 7.03 (d, $J=7.7\text{Hz}$, 2H), 5.05 (m, 1H), 4.59 (s, 2H), 4.13 (m, 2H), 3.79 (dd, $J=3.2\text{Hz}$, $J=14.5\text{Hz}$, 1H), 3.63 (dd, $J=10.0\text{Hz}$, $J=14.5\text{Hz}$, 1H). MS: (M^++1) 544;

Quinoline-3-carboxylic acid {(*R*)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide (Compound 57); ^1H NMR: (DMSO) 9.40 (d, $J=8.2\text{Hz}$, 1H), 9.30 (d, $J=2.2\text{Hz}$, 1H), 8.95 (t, $J=5.4\text{Hz}$, 1H), 8.84 (d, $J=2.0\text{Hz}$, 1H), 8.12 (dd, $J=3.7\text{Hz}$, $J=7.9\text{Hz}$, 2H), 7.89 (t, $J=7.4\text{Hz}$, 1H), 7.71 (t, $J=7.7\text{Hz}$, 1H), 7.54-7.44 (m, 2H), 7.32-7.23 (m, 2H), 7.14 (t, $J_{\text{H},\text{F}}=74\text{Hz}$, 1H), 5.17 (m, 1H), 4.65 (s, 2H), 4.17 (m, 2H), 3.88 (dd, $J=3.0\text{Hz}$, $J=14.5\text{Hz}$, 1H), 3.63 (dd, $J=10.0\text{Hz}$, $J=14.5\text{Hz}$, 1H). MS: (M^++1) 503;

N-(*R*)-1-(Cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-

phenylmethane-sulfonyl]-ethyl}-3-(1-phenyl-methanoyl)-benzamide (Compound 58); ^1H NMR: (DMSO) 9.22 (d, $J=8.2\text{Hz}$, 1H), 8.87 (t, $J=5.4\text{Hz}$, 1H), 8.27 (s, 1H), 8.17 (d, $J=7.9\text{Hz}$, 1H), 7.90 (d, $J=7.9\text{Hz}$, 1H), 7.78-7.66 (m, 4H), 7.59-7.44 (m, 4H), 7.32-7.23 (m, 2H), 7.13 (t, $J_{\text{H},\text{F}}=74\text{Hz}$, 1H), 5.09 (m, 1H), 4.61 (s, 2H), 4.14 (m, 2H), 3.82 (dd, $J=3.2\text{Hz}$, $J=14.5\text{Hz}$, 1H), 3.65 (dd, $J=10.0\text{Hz}$, $J=14.5\text{Hz}$, 1H). MS: (M^++1) 556;

4-Chloro-*N*-(*R*)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenyl-methanesulfonyl]-ethyl}-benzamide (Compound 59); ^1H NMR: (DMSO) 9.08 (d, $J=8.2\text{Hz}$, 1H), 8.84 (t, $J=5.4\text{Hz}$, 1H), 7.89 (d, $J=8.4\text{Hz}$, 2H), 7.58 (d, $J=8.4\text{Hz}$, 2H), 7.52-7.44 (m, 2H), 7.32-7.23 (m, 2H), 7.13 (t, $J_{\text{H},\text{F}}=74\text{Hz}$, 1H), 5.07 (m, 1H), 4.60 (s, 2H), 4.14 (m, 2H), 3.81 (dd, $J=3.2\text{Hz}$, $J=14.5\text{Hz}$, 1H), 3.63 (dd, $J=10.0\text{Hz}$, $J=14.5\text{Hz}$, 1H). MS: (M^++1) 486, 488;

N-(*R*)-1-(Cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethane-sulfonyl]-ethyl}-3-fluoro-4-methoxy-benzamide (Compound 60); ^1H NMR: (DMSO) 8.94 (d, $J=8.2\text{Hz}$, 1H), 8.83 (t, $J=5.4\text{Hz}$, 1H), 7.75-7.68 (m, 2H), 7.52-7.44 (m, 2H), 7.32-7.23 (m, 3H), 7.13 (t, $J_{\text{H},\text{F}}=74\text{Hz}$, 1H), 5.05 (m, 1H), 4.59 (s, 2H), 4.13 (m, 2H), 3.90 (s, 3H), 3.80 (dd, $J=3.2\text{Hz}$, $J=14.5\text{Hz}$, 1H), 3.62 (dd, $J=10.0\text{Hz}$, $J=14.5\text{Hz}$, 1H). MS: (M^++1) 500;

3-Bromo-thiophene-2-carboxylic acid {(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide (Compound 61); ¹H

NMR: (DMSO) 8.89 (t, J=5.4Hz, 1H), 8.59 (d, J=8.2Hz, 1H), 7.86 (d, J=5.2Hz, 1H), 7.53-7.44 (m, 2H), 7.32-7.23 (m, 2H), 7.21 (d, J=5.2Hz, 1H), 7.13 (t, J_{H,F}=74Hz, 1H),

5 5.04 (m, 1H), 4.61 (s, 2H), 4.16 (m, 2H), 3.79 (dd, J=3.5Hz, J=14.5Hz, 1H), 3.70 (dd, J=9.0Hz, J=14.5Hz, 1H). MS: (M⁺+1) 536, 538;

3-Chloro-benzo[b]thiophene-2-carboxylic acid {(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide

(Compound 62); ¹H NMR: (DMSO) 8.96 (t, J=5.4Hz, 1H), 8.82 (d, J=8.2Hz, 1H),

10 8.17-8.10 (m, 1H), 7.96-7.89 (m, 1H), 7.64-7.56 (m, 2H), 7.54-7.44 (m, 2H), 7.32-7.23 (m, 2H), 7.14 (t, J_{H,F}=74Hz, 1H), 5.14 (m, 1H), 4.64 (s, 2H), 4.19 (m, 2H), 3.88-3.73 (m, 2H). MS: (M⁺+1) 542, 544;

3-Chloro-thiophene-2-carboxylic acid {(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide (Compound 63); ¹H

15 NMR: (DMSO) 8.88 (t, J=5.4Hz, 1H), 8.49 (d, J=8.2Hz, 1H), 7.90 (d, J=5.4Hz, 1H), 7.52-7.44 (m, 2H), 7.32-7.23 (m, 2H), 7.18 (d, J=5.4Hz, 1H), 7.13 (t, J_{H,F}=74Hz, 1H), 5.05 (m, 1H), 4.61 (s, 2H), 4.16 (m, 2H), 3.82-3.70 (m, 2H). MS: (M⁺+1) 492, 494;

N-[(R)-(Cyanomethyl-carbamoyl)-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl]-trifluoromethyl-benzamide (Compound 64); ¹H NMR:

20 (DMSO) 9.24 (d, J=8.2Hz, 1H), 8.88 (t, J=5.4Hz, 1H), 8.07 (d, J=8.2Hz, 2H), 7.90 (d, J=8.4Hz, 2H), 7.53-7.44 (m, 2H), 7.32-7.23 (m, 2H), 7.13 (t, J_{H,F}=74Hz, 1H), 5.11 (m, 1H), 4.62 (s, 2H), 4.15 (m, 2H), 3.83 (dd, J=3.2Hz, J=14.5Hz, 1H), 3.64 (dd, J=10.0Hz, J=14.5Hz, 1H). MS: (M⁺+1) 520;

Quinoline-2-carboxylic acid {(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-

25 difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide (Compound 65); ¹H NMR: (DMSO) 9.51 (d, J=8.2Hz, 1H), 8.85 (t, J=5.4Hz, 1H), 8.60 (d, J=8.4Hz, 1H), 8.20 (d, J=8.4Hz, 1H), 8.16-8.08 (m, 2H), 7.89 (t, J=7.0Hz, 1H), 7.74 (t, J=7.0Hz, 1H), 7.53-7.44 (m, 2H), 7.32-7.23 (m, 2H), 7.11 (t, J_{H,F}=74Hz, 1H), 5.21 (m, 1H), 4.62 (s, 2H), 4.14 (m, 2H), 4.00-3.82 (m, 2H). MS: (M⁺+1) 503;

30 (R)-2-Benzenesulfonylamino-N-cyanomethyl-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-propionamide (Compound 66); ¹H NMR: (DMSO) 9.02 (t,

J=5.4Hz, 1H), 8.57 (d, J=9.2Hz, 1H), 8.77 (m, 2H), 7.65-7.23 (m, 7H), 7.11 (t, J_{H,F}=74Hz, 1H), 4.52 (d, J=13.6Hz, 1H), 4.44 (d, J=13.6Hz, 1H), 4.38 (m, 1H), 4.01-3.85 (m, 2H), 3.47 (dd, J=5.9Hz, J=14.5Hz, 1H), 3.22 (dd, J=7.2Hz, J=14.5Hz, 1H).

MS: (M⁺+1) 488;

5 (R)-N-Cyanomethyl-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-(naphthalene-2-sulfonylamino)-propionamide (Compound 67); ¹H NMR: (DMSO) 9.05 (t, J=5.4Hz, 1H), 8.67 (d, J=9.0Hz, 1H), 8.43 (s, 1H), 8.14-8.01 (m, 3H), 7.78 (dd, J=2.0Hz, J=8.6Hz, 1H), 7.74-6.63 (m, 2H), 7.46-7.39 (m, 1H), 7.27-7.14 (m, 3H), 7.07 (t, J_{H,F}=74Hz, 1H), 4.52-4.37 (m, 3H), 3.86 (m, 2H), 3.49 (dd, J=5.7Hz, J=14.5Hz, 1H), 10 3.26 (dd, J=7.2Hz, J=14.5Hz, 1H). MS: (M⁺+1) 538;

10 (R)-N-Cyanomethyl-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-(thiophene-2-sulfonylamino)-propionamide (Compound 68); ¹H NMR: (DMSO) 9.06 (t, J=5.4Hz, 1H), 8.78 (d, J=9.1Hz, 1H), 7.91 (d, J=4.9Hz, 1H), 7.57 (d, J=3Hz, 1H), 7.51-7.40 (m, 2H), 7.32-7.23 (m, 2H), 7.12 (m, 1H), 7.11 (t, J_{H,F}=74Hz, 1H), 4.54 (d, J=13.8Hz, 1H), 4.47 (d, J=13.8Hz, 1H), 4.42 (m, 1H), 4.10-3.95 (m, 2H), 3.50 (dd, J=5.9Hz, J=14.5Hz, 1H), 3.24 (dd, J=7.2Hz, J=14.5Hz, 1H). MS: (M⁺+1) 494;

15 Cyclopentanecarboxylic acid {(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide (Compound 69); ¹H NMR: (DMSO) 8.69 (t, J=5.4Hz, 1H), 8.34 (d, J=8.4Hz, 1H), 7.52-7.44 (m, 2H), 7.33-7.23 (m, 2H), 7.14 (t, J_{H,F}=74Hz, 1H), 4.84 (m, 1H), 4.56 (s, 2H), 4.12 (m, 2H), 3.67 (dd, J=3.9Hz, J=14.5Hz, 1H), 3.41 (dd, J=9.2Hz, J=14.5Hz, 1H), 2.62 (m, 1H), 1.76-1.45 (m, 8H). MS: (M⁺+1) 444; and

20 Morpholine-4-carboxylic acid {(R)-1-[(1-cyano-1-thiophen-2-yl-methyl)-carbamoyl]-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide (Compound 70) ¹H-NMR (CDCl₃) δ (ppm): 8.37, 8.34 (pair of d, J=3.7Hz, 1H); 7.49-7.18 (m, 4H); 6.99, 6.97 (pair of d, J=3.5Hz, 1H), 6.54, 6.53 (pair of t, J=72.3Hz, 1H), 6.14 (m, 1H), 5.92 (m, 1H), 4.95 (m, 1H), 4.48 (m, 2H), 3.75-3.58 (m, 5H), 3.50-3.40 (m, 1H), 3.31 (m, 4H); MS (M⁺) = 543.2 (M⁻) = 540.8.

Solutions of test compounds in varying concentrations were prepared in 10 μ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: MES, 50 mM (pH 6.5); EDTA, 2.5 mM; and NaCl, 100 mM). Human cathepsin S
5 (0.158 pMoles in 25 μ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient temperature. Z-Val-Val-Arg-AMC (9 nMoles in 25 μ L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the
10 enzyme progress curves using standard mathematical models.

EXAMPLE 6

Cathepsin B Assay

15 Solutions of test compounds in varying concentrations were prepared in 10 μ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid (BES), 50 mM (pH 6); polyoxyethylenesorbitan monolaurate, 0.05%; and dithiothreitol (DTT), 2.5 mM). Human cathepsin B (0.025 pMoles in 25 μ L of assay buffer) was added to the dilutions.
20 The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient temperature. Z-FR-AMC (20 nMoles in 25 μ L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.
25

EXAMPLE 7

Cathepsin K Assay

Solutions of test compounds in varying concentrations were prepared in 10 μ L of
30 dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: MES,

50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin K (0.0906 pMoles in 25 μ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient temperature. Z-Phe-Arg-AMC (4 nMoles in 25 μ L of assay buffer) was added to the assay 5 solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

EXAMPLE 8

10 Cathepsin L Assay

Solutions of test compounds in varying concentrations were prepared in 10 μ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: MES, 50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin L (0.05 pMoles 15 in 25 μ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient temperature. Z-Phe-Arg-AMC (1 nMoles in 25 μ L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using 20 standard mathematical models.

Compounds of the invention were tested according to the above-described assays for protease inhibition and observed to exhibit selective cathepsin S inhibitory activity. For example, the compounds of the invention were found to inhibit cathepsin S protease 25 activity at concentrations that are least 50 fold less than those concentrations required to produce an equiactive inhibition of cathepsin K protease activity. The apparent inhibition constants (K_i) for the compounds of the invention, against Cathepsin S, are from about 10^{-10} M to about 10^{-7} M.

EXAMPLE 9

Representative Pharmaceutical Formulations Containing a Compound of Formula
I

ORAL FORMULATION

5	Compound of Formula I	10-100 mg
	Citric Acid Monohydrate	105 mg
	Sodium Hydroxide	18 mg
	Flavoring	
	Water	q.s. to 100 mL

10

INTRAVENOUS FORMULATION

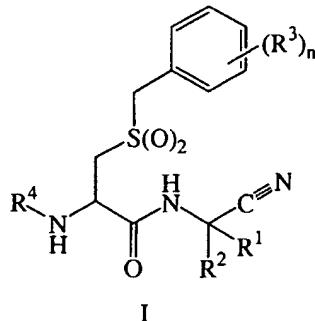
15	Compound of Formula I	0.1-10 mg
	Dextrose Monohydrate	q.s. to make isotonic
	Citric Acid Monohydrate	1.05 mg
	Sodium Hydroxide	0.18 mg
	Water for Injection	q.s. to 1.0 mL

TABLET FORMULATION

20	Compound of Formula I	1%
	Microcrystalline Cellulose	73%
	Stearic Acid	25%
	Colloidal Silica	1%.

WE CLAIM:

1. A compound of Formula I:



5

in which:

n is 1, 2, 3, 4 or 5;

R¹ is hydrogen and R² is cyano, hetero(C₅)aryl or (C₁₋₄)alkyl-substituted hetero(C₅)aryl or both R¹ and R² are hydrogen, halo, (C₁₋₄)alkyl or -X¹OR⁵, wherein X¹ and R⁵ are as defined below, or R¹ and R² together with the carbon atom to which both R¹ and R² are attached form (C₃₋₈)cycloalkylene or (C₃₋₈)heterocycloalkylene;

R³ at the first occurrence is selected from a group consisting of nitro, -X¹NR⁵R⁵, -X¹SR⁵, -X¹C(O)NR⁵R⁵, -X¹C(O)OR⁵, -X¹S(O)R⁶, -X¹S(O)₂R⁶, -X¹C(O)R⁶ and -X¹OR⁷, wherein X¹ is a bond or (C₁₋₂)alkylene, R⁵ at each occurrence independently is hydrogen, (C₁₋₃)alkyl or halo-substituted (C₁₋₃)alkyl, R⁶ is (C₁₋₃)alkyl or halo-substituted (C₁₋₃)alkyl and R⁷ is halo-substituted (C₁₋₃)alkyl and R³ at each other occurrence, if present, independently is selected from a group consisting of (C₁₋₄)alkyl, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X¹NR⁵R⁵, -X¹OR⁵, -X¹SR⁵, -X¹C(O)NR⁵R⁵, -X¹C(O)OR⁵, -X¹S(O)R⁶, -X¹S(O)₂R⁶ and -X¹C(O)R⁶, wherein X¹, R⁵ and R⁶ are as defined above; and

R⁴ is -C(O)X²R⁸ or -S(O)₂X²R⁸, wherein X² is a bond, -O- or -NR⁹-, wherein R⁹ is hydrogen or (C₁₋₆)alkyl, and R⁸ is (i) (C₁₋₆)alkyl optionally substituted by -OR¹⁰, -SR¹⁰, -S(O)R¹⁰, -S(O)₂R¹⁰, -C(O)R¹⁰, -C(O)OR¹⁰, -C(O)NR¹⁰R¹¹, -NR¹⁰R¹¹, -NR¹¹C(O)R¹⁰, -NR¹¹C(O)OR¹⁰, -NR¹¹C(O)NR¹⁰R¹¹ or 25 -NR¹¹C(NR¹¹)NR¹⁰R¹¹, wherein R¹⁰ is (C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl,

hetero(C₅₋₁₂)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₂)aryl(C₀₋₃)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₃)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₃)alkyl and R¹¹ at each occurrence independently is hydrogen or (C₁₋₆)alkyl, or (ii) C₃₋₁₂cycloalkyl(C₀₋₃)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₂)aryl(C₀₋₃)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl,

5 (C₉₋₁₂)bicycloaryl(C₀₋₃)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₃)alkyl or (iii) (C₃₋₆)cycloalkyl(C₀₋₃)alkyl, hetero(C₅₋₆)cycloalkyl(C₀₋₃)alkyl, phenyl(C₀₋₃)alkyl or hetero(C₅₋₆)aryl(C₀₋₃)alkyl substituted by -X³OR¹², -X³SR¹², -X³S(O)R¹², -X³S(O)₂R¹², -X³C(O)R¹², -X³C(O)OR¹², -X³C(O)NR¹²R¹³, -X³NR¹²R¹³, -X³NR¹³C(O)R¹², -X³NR¹³C(O)OR¹², -X³NR¹³C(O)NR¹²R¹³ or

10 -X³NR¹³C(NR¹³)NR¹²R¹³, wherein X³ is a bond or methylene, R¹² is (C₃₋₆)cycloalkyl(C₀₋₃)alkyl, hetero(C₅₋₆)cycloalkyl(C₀₋₃)alkyl, phenyl(C₀₋₃)alkyl or hetero(C₅₋₆)aryl(C₀₋₃)alkyl and R¹³ is hydrogen or (C₁₋₆)alkyl; wherein R⁴ optionally further contains 1 to 5 substituents which when occurring within an alicyclic or aromatic ring system are radicals independently selected from a group consisting of

15 (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₃)alkyl, nitro, -X⁴NR¹⁴R¹⁴, -X⁴NR¹⁴C(O)OR¹⁴, -X⁴NR¹⁴C(O)NR¹⁴R¹⁴, -X⁴NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -X⁴OR¹⁴, -X⁴SR¹⁴, -X⁴C(O)OR¹⁴, -X⁴C(O)NR¹⁴R¹⁴, -X⁴S(O)₂NR¹⁴R¹⁴, -X⁴P(O)(OR¹⁴)OR¹⁴, -X⁴OP(O)(OR¹⁴)OR¹⁴, -X⁴NR¹⁴C(O)R¹⁴, -X⁴S(O)R¹⁵, -X⁴S(O)₂R¹⁵ and -X⁴C(O)R¹⁵ and when occurring within an aliphatic moiety are

20 radicals independently selected from a group consisting of cyano, halo, nitro, -NR¹⁴R¹⁴, -NR¹⁴C(O)OR¹⁴, -NR¹⁴C(O)NR¹⁴R¹⁴, -NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -OR¹⁴, -SR¹⁴, -C(O)OR¹⁴, -C(O)NR¹⁴R¹⁴, -S(O)₂NR¹⁴R¹⁴, -P(O)(OR¹⁴)OR¹⁴, -OP(O)(OR¹⁴)OR¹⁴, -NR¹⁴C(O)R¹⁵, -S(O)R¹⁵, -S(O)₂R¹⁵ and -C(O)R¹⁵, wherein X⁴ is a bond or (C₁₋₆)alkylene, R¹⁴ at each occurrence independently is hydrogen, (C₁₋₆)alkyl or

25 halo-substituted (C₁₋₃)alkyl and R¹⁵ is (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl; and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

2. The compound of Claim 1 in which n is 1 or 2, R¹ is hydrogen and R⁴ is hydrogen, hetero(C₅)aryl or (C₁₋₄)alkyl-substituted hetero(C₅)aryl or R¹ and R² together with the carbon atom to which both R¹ and R² are attached form (C₃₋₅)cycloalkylene or (C₅₋₆)heterocycloalkylene, R³ at the first occurrence is selected from a group consisting of difluoromethoxy, trifluoromethoxy, trifluorosulfanyl and nitro and R³ at the second occurrence, if present, is selected from a group consisting of (C₁₋₄)alkyl, bromo, carboxy, chloro, cyano, difluoromethoxy, fluoro, iodo, methoxy, nitro, trifluoromethoxy, trifluoromethyl and trifluorosulfanyl and R⁴ is -C(O)X²R⁸ or -S(O)₂X²R⁸, wherein X² is a bond, -O- or -NR⁹-, wherein R⁹ is hydrogen or (C₁₋₆)alkyl, and R⁸ is (C₁₋₆)alkyl, (C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₀)aryl(C₀₋₃)alkyl, hetero(C₅₋₁₀)aryl(C₀₋₃)alkyl, hetero(C₈₋₁₂)bicycloaryl(C₀₋₃)alkyl, or phenyl(C₀₋₃)alkyl, wherein the phenyl is substituted by -X³OR¹² or -X³C(O)R¹², wherein X³ is a bond or methylene and R¹² is phenyl(C₀₋₃)alkyl, wherein any aryl or heteroaryl group comprising R⁴ optionally is substituted in the ring by 1 to 2 substituents selected from (C₁₋₆)alkyl, halo, halo-substituted (C₁₋₃)alkyl, -X⁴NR¹⁴R¹⁴ and -X⁴OR¹⁴, wherein X⁴ is a bond or (C₁₋₆)alkylene, R¹⁴ is hydrogen, (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl; and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

3. The compound of Claim 2 in which R³ at the first occurrence is nitro or difluoromethoxy in the ortho or meta position and R⁴ is allyloxycarbonyl, 2-aminopyridinylcarbonyl, benzo[1,3]dioxolylcarbonyl, benzothienyl, benzoyl, 3-benzoylbenzoyl, 4-bromobenzoyl, 3-bromothienyl, biphenylylcarbonyl, 3-chlorobenzothienyl, 4-chlorobenzoyl, 3-chlorothienyl, cyclopentylcarbonyl, 3,4-difluorobenzoyl, dimethylcarbamoyl, 3,4-dimethoxybenzoyl, 4-fluorobenzoyl, 3-fluoro-4-hydroxybenzoyl, 2-hydroxypyridinylcarbonyl, 3-hydroxypyridinylcarbonyl, indolylcarbonyl, isobutyloxycarbonyl, isopropylcarbamoyl, isopropyloxycarbonyl, 4-methoxybenzoyl, methoxycarbonyl, 3-methylbenzoyl, 2-methylthienylcarbonyl,

4-methylvaleryl, morpholin-1-ylcarbonyl, naphthalenylcarbonyl, naphthalenylsulfonyl, phenoxy carbonyl, phenylacryloyl, phenylsulfonyl, pyrazinylcarbonyl, pyridinylcarbonyl, quinolyl, thienylcarbonyl, thienylsulfonyl, 4-trifluoromethoxybenzoyl or

4-trifluoromethylbenzoyl; and the *N*-oxide derivatives, prodrug derivatives, protected

5 derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

10 4. The compound of Claim 2 in which R^3 at the first occurrence is nitro or difluoromethoxy in the ortho position and R^4 is benzoyl, indolyl,

morpholin-4-ylcarbonyl, thienylcarbonyl or pyridinylcarbonyl optionally substituted in the ring by 1 to 2 substituents selected from fluoro and methyl; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures

15 of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

5. The compound of Claim 4 selected from a group consisting of:

20 *N*-[1*R*-cyanomethylcarbamoyl-2-(2-difluoromethoxybenzylsulfonyl)ethyl]-morpholine-4-carboxamide;

thiophene-2-carboxylic acid-{(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide;

25 thiophene-3-carboxylic acid-{(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide;

N-{(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-4-fluoro-benzamide;

morpholine-4-carboxylic acid-{(R)-1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide;

30 5-methyl-thiophene-2-carboxylic acid-{(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide;

1H-indole-5-carboxylic acid-{(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-amide;
N-{(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-3-methyl-benzamide;
5 N-{(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-3,4-difluoro-benzamide;
N-{(R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl}-isonicotinamide;
N-[1R-(1-cyanocyclopropylcarbamoyl)-2-(2-difluoromethoxybenzylsulfonyl)-ethyl]morpholine-4-carboxamide; and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

15

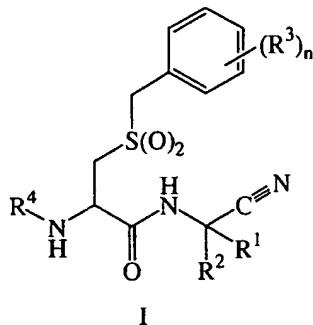
6. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 in combination with a pharmaceutically acceptable excipient.

20

7. A method for treating a disease in an animal in which inhibition of cathepsin S can prevent, inhibit or ameliorate the pathology and/or symptomatology of the disease, which method comprises administering to the animal a therapeutically effective amount of compound of Claim 1 or a N-oxide derivative or individual isomer or mixture of isomers thereof; or a pharmaceutically acceptable salt or solvate of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

25

8. The use of a compound of Formula I:



in which:

n is 1, 2, 3, 4 or 5;

5 R¹ is hydrogen and R² is cyano, hetero(C₅)aryl or (C₁₋₄)alkyl-substituted hetero(C₅)aryl or both R¹ and R² are hydrogen, halo, (C₁₋₄)alkyl or -X¹OR⁵, wherein X¹ and R⁵ are as defined below, or R¹ and R² together with the carbon atom to which both R¹ and R² are attached form (C₃₋₈)cycloalkylene or (C₃₋₈)heterocycloalkylene;

R³ at the first occurrence is selected from a group consisting of nitro,

10 -X¹NR⁵R⁵, -X¹SR⁵, -X¹C(O)NR⁵R⁵, -X¹C(O)OR⁵, -X¹S(O)R⁶, -X¹S(O)₂R⁶,
-X¹C(O)R⁶ and -X¹OR⁷, wherein X¹ is a bond or (C₁₋₂)alkylene, R⁵ at each occurrence independently is hydrogen, (C₁₋₃)alkyl or halo-substituted (C₁₋₃)alkyl, R⁶ is (C₁₋₃)alkyl or halo-substituted (C₁₋₃)alkyl and R⁷ is halo-substituted (C₁₋₃)alkyl and R³ at each other occurrence, if present, independently is selected from a group consisting of (C₁₋₄)alkyl, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X¹NR⁵R⁵, -X¹OR⁵, -X¹SR⁵,
-X¹C(O)NR⁵R⁵, -X¹C(O)OR⁵, -X¹S(O)R⁶, -X¹S(O)₂R⁶ and -X¹C(O)R⁶, wherein X¹, R⁵ and R⁶ are as defined above; and

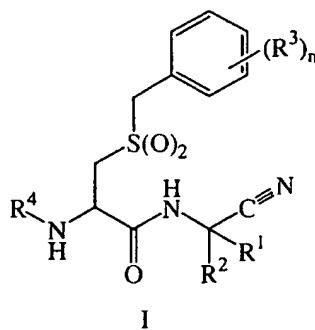
R⁴ is -C(O)X²R⁸ or -S(O)₂X²R⁸, wherein X² is a bond, -O- or -NR⁹-,

wherein R⁹ is hydrogen or (C₁₋₆)alkyl, and R⁸ is (i) (C₁₋₆)alkyl optionally substituted by

20 -OR¹⁰, -SR¹⁰, -S(O)R¹⁰, -S(O)₂R¹⁰, -C(O)R¹⁰, -C(O)OR¹⁰, -C(O)NR¹⁰R¹¹,
-NR¹⁰R¹¹, -NR¹¹C(O)R¹⁰, -NR¹¹C(O)OR¹⁰, -NR¹¹C(O)NR¹⁰R¹¹ or
-NR¹¹C(NR¹¹)NR¹⁰R¹¹, wherein R¹⁰ is (C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₂)aryl(C₀₋₃)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₃)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₃)alkyl and R¹¹ at each occurrence independently is hydrogen or (C₁₋₆)alkyl, or (ii) C₃₋₁₂cycloalkyl(C₀₋₃)alkyl,

hetero(C₅₋₁₂)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₂)aryl(C₀₋₃)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₃)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₃)alkyl or (iii) (C₃₋₆)cycloalkyl(C₀₋₃)alkyl, hetero(C₅₋₆)cycloalkyl(C₀₋₃)alkyl, phenyl(C₀₋₃)alkyl or hetero(C₅₋₆)aryl(C₀₋₃)alkyl substituted by -X³OR¹², -X³SR¹², -X³S(O)R¹², -X³S(O)₂R¹², -X³C(O)R¹², -X³C(O)OR¹², -X³C(O)NR¹²R¹³, -X³NR¹²R¹³, -X³NR¹³C(O)R¹², -X³NR¹³C(O)OR¹², -X³NR¹³C(O)NR¹²R¹³ or -X³NR¹³C(NR¹³)NR¹²R¹³, wherein X³ is a bond or methylene, R¹² is (C₃₋₆)cycloalkyl(C₀₋₃)alkyl, hetero(C₅₋₆)cycloalkyl(C₀₋₃)alkyl, phenyl(C₀₋₃)alkyl or hetero(C₅₋₆)aryl(C₀₋₃)alkyl and R¹³ is hydrogen or (C₁₋₆)alkyl; wherein R⁴ optionally further contains 1 to 5 substituents which when occurring within an alicyclic or aromatic ring system are radicals independently selected from a group consisting of (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, nitro, halo-substituted (C₁₋₃)alkyl, -X⁴NR¹⁴R¹⁴, -X⁴NR¹⁴C(O)OR¹⁴, -X⁴NR¹⁴C(O)NR¹⁴R¹⁴, -X⁴NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -X⁴OR¹⁴, -X⁴SR¹⁴, -X⁴C(O)OR¹⁴, -X⁴C(O)NR¹⁴R¹⁴, -X⁴S(O)₂NR¹⁴R¹⁴, -X⁴P(O)(OR¹⁴)OR¹⁴, -X⁴OP(O)(OR¹⁴)OR¹⁴, -X⁴NR¹⁴C(O)R¹⁴, -X⁴S(O)R¹⁵, -X⁴S(O)₂R¹⁵ and -X⁴C(O)R¹⁵ and when occurring within an aliphatic moiety are radicals independently selected from a group consisting of cyano, halo, nitro, -NR¹⁴R¹⁴, -NR¹⁴C(O)OR¹⁴, -NR¹⁴C(O)NR¹⁴R¹⁴, -NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -OR¹⁴, -SR¹⁴, -C(O)OR¹⁴, -C(O)NR¹⁴R¹⁴, -S(O)₂NR¹⁴R¹⁴, -P(O)(OR¹⁴)OR¹⁴, -OP(O)(OR¹⁴)OR¹⁴, -NR¹⁴C(O)R¹⁵, -S(O)R¹⁵, -S(O)₂R¹⁵ and -C(O)R¹⁵, wherein X⁴ is a bond or (C₁₋₆)alkylene, R¹⁴ at each occurrence independently is hydrogen, (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl and R¹⁵ is (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl; and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; in the manufacture of a medicament for treating a disease in an animal in which cathepsin S activity contributes to the pathology and/or symptomatology of the disease.

30 9. A process for preparing a compound of Formula I:



in which:

5 n is 1, 2, 3, 4 or 5;

 R¹ is hydrogen and R² is cyano, hetero(C₅)aryl or (C₁₋₄)alkyl-substituted hetero(C₅)aryl or both R¹ and R² are hydrogen, halo, (C₁₋₄)alkyl or -X¹OR⁵, wherein X¹ and R⁵ are as defined below, or R¹ and R² together with the carbon atom to which both R¹ and R² are attached form (C₃₋₈)cycloalkylene or (C₃₋₈)heterocycloalkylene;

10 R³ at the first occurrence is selected from a group consisting of nitro, -X¹NR⁵R⁵, -X¹SR⁵, -X¹C(O)NR⁵R⁵, -X¹C(O)OR⁵, -X¹S(O)R⁶, -X¹S(O)₂R⁶, -X¹C(O)R⁶ and -X¹OR⁷, wherein X¹ is a bond or (C₁₋₂)alkylene, R⁵ at each occurrence independently is hydrogen, (C₁₋₃)alkyl or halo-substituted (C₁₋₃)alkyl, R⁶ is (C₁₋₃)alkyl or halo-substituted (C₁₋₃)alkyl and R⁷ is halo-substituted (C₁₋₃)alkyl and R³ at each other occurrence, if present, independently is selected from a group consisting of (C₁₋₄)alkyl, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X¹NR⁵R⁵, -X¹OR⁵, -X¹SR⁵, -X¹C(O)NR⁵R⁵, -X¹C(O)OR⁵, -X¹S(O)R⁶, -X¹S(O)₂R⁶ and -X¹C(O)R⁶, wherein X¹, R⁵ and R⁶ are as defined above; and

 R⁴ is -C(O)X²R⁸ or -S(O)₂X²R⁸, wherein X² is a bond, -O- or -NR⁹-, wherein R⁹ is hydrogen or (C₁₋₆)alkyl, and R⁸ is (i) (C₁₋₆)alkyl optionally substituted by -OR¹⁰, -SR¹⁰, -S(O)R¹⁰, -S(O)₂R¹⁰, -C(O)R¹⁰, -C(O)OR¹⁰, -C(O)NR¹⁰R¹¹, -NR¹⁰R¹¹, -NR¹¹C(O)R¹⁰, -NR¹¹C(O)OR¹⁰, -NR¹¹C(O)NR¹⁰R¹¹ or -NR¹¹C(NR¹¹)NR¹⁰R¹¹, wherein R¹⁰ is (C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₂)aryl(C₀₋₃)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₃)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₃)alkyl and R¹¹ at each

occurrence independently is hydrogen or (C₁₋₆)alkyl, or (ii) C₃₋₁₂cycloalkyl(C₀₋₃)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₂)aryl(C₀₋₃)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₃)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₃)alkyl or (iii) (C₃₋₆)cycloalkyl(C₀₋₃)alkyl, hetero(C₅₋₆)cycloalkyl(C₀₋₃)alkyl, phenyl(C₀₋₃)alkyl or

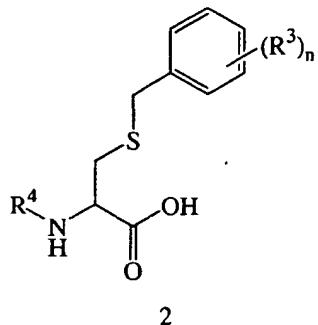
5 hetero(C₅₋₆)aryl(C₀₋₃)alkyl substituted by -X³OR¹², -X³SR¹², -X³S(O)R¹², -X³S(O)₂R¹², -X³C(O)R¹², -X³C(O)OR¹², -X³C(O)NR¹²R¹³, -X³NR¹²R¹³, -X³NR¹³C(O)R¹², -X³NR¹³C(O)OR¹², -X³NR¹³C(O)NR¹²R¹³ or -X³NR¹³C(NR¹³)NR¹²R¹³, wherein X³ is a bond or methylene, R¹² is

10 (C₃₋₆)cycloalkyl(C₀₋₃)alkyl, hetero(C₅₋₆)cycloalkyl(C₀₋₃)alkyl, phenyl(C₀₋₃)alkyl or hetero(C₅₋₆)aryl(C₀₋₃)alkyl and R¹³ is hydrogen or (C₁₋₆)alkyl; wherein R⁴ optionally further contains 1 to 5 substituents which when occurring within an alicyclic or aromatic ring system are radicals independently selected from a group consisting of (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, nitro, halo-substituted (C₁₋₃)alkyl, -X⁴NR¹⁴R¹⁴, -X⁴NR¹⁴C(O)OR¹⁴, -X⁴NR¹⁴C(O)NR¹⁴R¹⁴, -X⁴NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴,

15 -X⁴OR¹⁴, -X⁴SR¹⁴, -X⁴C(O)OR¹⁴, -X⁴C(O)NR¹⁴R¹⁴, -X⁴S(O)₂NR¹⁴R¹⁴, -X⁴P(O)(OR¹⁴)OR¹⁴, -X⁴OP(O)(OR¹⁴)OR¹⁴, -X⁴NR¹⁴C(O)R¹⁴, -X⁴S(O)R¹⁵, -X⁴S(O)₂R¹⁵ and -X⁴C(O)R¹⁵ and when occurring within an aliphatic moiety are radicals independently selected from a group consisting of cyano, halo, nitro, -NR¹⁴R¹⁴, -NR¹⁴C(O)OR¹⁴, -NR¹⁴C(O)NR¹⁴R¹⁴, -NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -OR¹⁴, -SR¹⁴, -C(O)OR¹⁴, -C(O)NR¹⁴R¹⁴, -S(O)₂NR¹⁴R¹⁴, -P(O)(OR¹⁴)OR¹⁴, -OP(O)(OR¹⁴)OR¹⁴, -NR¹⁴C(O)R¹⁵, -S(O)R¹⁵, -S(O)₂R¹⁵ and -C(O)R¹⁵, wherein X⁴ is a bond or (C₁₋₆)alkylene, R¹⁴ at each occurrence independently is hydrogen, (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl and R¹⁵ is (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl; and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and

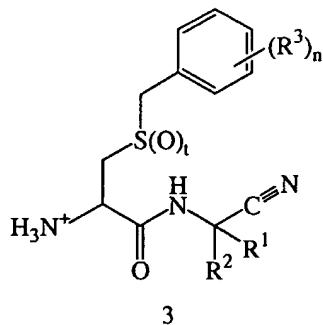
20 mixtures of isomers thereof; and the pharmaceutically acceptable salts thereof; and the pharmaceutically acceptable salts thereof; which processes comprises:

25 (A) reacting a compound of Formula 2:



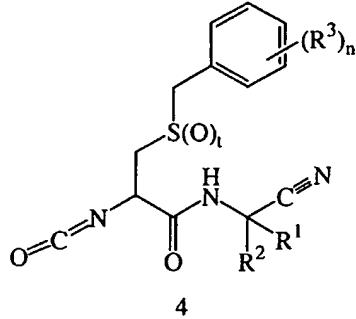
with a compound of the formula $\text{NH}_2\text{CR}^1\text{R}^2\text{CN}$, in which n , R^1 , R^2 , R^3 and R^4 are as defined above; or

5 (B) reacting a compound of Formula 3:



with a compound of the formula R^4L , in which t is 0 or 2, L is a leaving group and each 10 n , R^1 , R^2 , R^3 and R^4 are as defined above, and then oxidizing when n is 0; or

(C) reacting a compound of Formula 4:

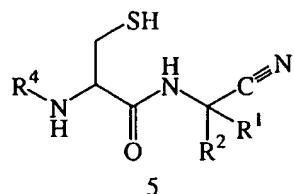


15 with a compound of formula $\text{NHR}^{10}\text{R}^{11}$ or $\text{NHR}^{16}\text{R}^{17}$ to provide a compound of Formula I in which R^4 is $-\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$ or $-\text{C}(\text{O})\text{NR}^{16}\text{R}^{17}$, respectively, wherein t is 0

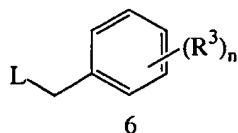
or 2, R¹⁶ and R¹⁷ together with the nitrogen atom to which R¹⁶ and R¹⁷ are attached form hetero(C₅₋₁₂)cycloalkyl and each n, R¹, R² and R³ are as defined above, and then oxidizing when t is 0; or

(D) reacting a compound of Formula 5:

5



with a compound of Formula 6:



10

in which L is a leaving group and each n, R¹, R², R³ and R⁴ are as defined above; and

(E) optionally converting a compound of Formula I into a pharmaceutically acceptable salt;

(F) optionally converting a salt form of a compound of Formula I to non-salt form;

15 (G) optionally converting an unoxidized form of a compound of Formula I into a pharmaceutically acceptable N-oxide;

(H) optionally converting an N-oxide form of a compound of Formula I its unoxidized form; and

(I) optionally resolving an individual isomer of a compound of Formula I from a

20 mixture of isomers.

INTERNATIONAL SEARCH REPORT

Interr Application No
PCT/US 00/25341

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D295/20 C07D211/66 C07D213/89 C07D213/82 C07D213/81
C07D241/24 C07D309/08 C07D333/38 C07D333/40 C07D209/08
C07D317/68 C07D333/70 C07D215/54 C07D215/48 C07C317/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 652 009 A (LILLY CO ELI ;ATHENA NEUROSCIENCES INC (US)) 10 May 1995 (1995-05-10) page 99, line 29 -page 100, line 4; claims 1-3; example 117 --- -/-	1,6-8

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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- *E* earlier document but published on or after the international filing date
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Date of the actual completion of the international search

12 December 2000

Date of mailing of the international search report

27/12/2000

Name and mailing address of the ISA

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Hass, C

INTERNATIONAL SEARCH REPORT

Inter. Application No
PCT/US 00/25341

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/5375 A61K31/5377 A61K31/455 A61K31/47 A61K31/4965
A61K31/381 A61P19/02 A61P33/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PICKEN P P ET AL: "Inhibition of bovine cathepsin B by amino acid-derived nitriles" BIOCHEMICAL SOCIETY TRANSACTIONS, COLCHESTER, ESSEX, GB, vol. 18, no. 2, April 1990 (1990-04), page 316 XP002108054 ISSN: 0300-5127 left-hand column, paragraph "Experimental", compound "benzyloxycarbonyl-L-(S-Benzyl)-cysteinyl- aminoacetonitrile" table 1 ---	1,7,8
A, P	WO 00 51998 A (BOEHRINGER INGELHEIM PHARMA) 8 September 2000 (2000-09-08) abstract; claims 21,31,45-49; examples 1,2 ---	1,6-8 -/-

Further documents are listed in the continuation of box C.

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Hass, C

INTERNATIONAL SEARCH REPORT

Intern'l Application No
PCT/US 00/25341

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 23588 A (BRITISH BIOTECH PHARM; FLOYD CHRISTOPHER DAVID (GB)) 4 June 1998 (1998-06-04) page 1, line 1 -page 2, line 3; claims 1,20; examples 3,6 ---	1,6-8
A	US 5 852 007 A (CHATTERJEE SANKAR) 22 December 1998 (1998-12-22) claims 1,32,38; example 66 ---	1,6-8
A	S. CHATTERJEE ET AL.: "D-Amino Acid Containing, High-Affinity Inhibitors of Recombinant Human Calpain I" JOURNAL OF MEDICINAL CHEMISTRY, vol. 41, no. 15, 16 July 1998 (1998-07-16), pages 2663-6, XP002155160 table 2, compound 23 -----	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/25341

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
EP 0652009	A 10-05-1995	AU	6897094	A	16-02-1995
		CA	2129689	A	10-02-1995
		CN	1120040	A	10-04-1996
		CZ	9401841	A	15-03-1995
		JP	7165606	A	27-06-1995
		NO	942883	A	10-02-1995
		NZ	264143	A	26-11-1996
		ZA	9405719	A	01-02-1996
WO 0051998	A 08-09-2000	NONE			
WO 9823588	A 04-06-1998	AU	5128298	A	22-06-1998
		EP	0944597	A	29-09-1999
US 5852007	A 22-12-1998	AU	714324	B	06-01-2000
		AU	1025397	A	03-07-1997
		CA	2238175	A	19-06-1997
		EP	0910564	A	28-04-1999
		WO	9721690	A	19-06-1997